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EXOPHTHALMOMETRIC MEASUREMENTS IN PATIENTS WITH THYROID DISEASES WITH SOME DISCUSSION OF THEIR SIGNIFICANCE *

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THE whole problem of the ophthalmopathy of Graves' disease of the classic and special varieties [1] has aroused much interest of late in this clinic. In order to get a comprehensive view of the degree of proptosis in various stages and types of the disease, actual exophthalmometric measurements have been made in 126 consecutive thyroid cases attending the Thyroid Clinic. The findings in these, and their significance, form the subject of this report.

METHOD

A modification, or elaboration of the Luedde ‡ exophthalmometer was employed (figure 1). Actually, two of these instruments, attached parallel to each other, were joined at right angles to the ends of two pieces of brass tubing, one of which could be telescoped into the other. Thus the exophthalmometers could be separated or approximated by sliding the tubing and at the same time kept in their parallel relationship. The notched end of each instrument is fitted to the bony angle of the outer margin of either orbit, and the whole held in place by digital pressure on the brass connecting piece. Readings are taken in the usual way for the instrument. The advantage of the double device is that error due to varying inclination of the line of measurement is avoided.

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‡ Manufactured by the E. B. Meyrowitz Company, New York City.

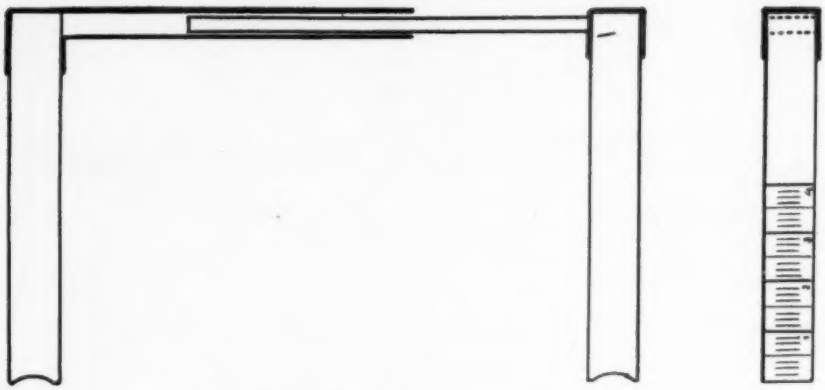

FIG. 1. The modified Luedde exophthalmometer.

CLINICAL MATERIAL

The results of measurements in the 126 cases are all shown in figures 2 and 3. It will be understood that the present study is in the nature of a

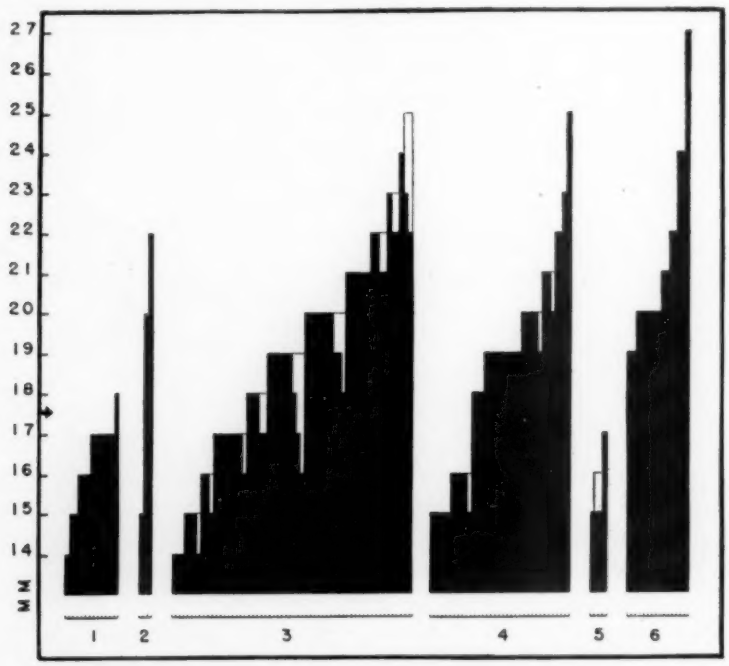

FIG. 2. The degree of proptosis in millimeters in patients is represented by the height of the columns. *Group 1.* Non-toxic nodular goiter. *Group 2.* Toxic nodular goiter. *Group 3.* Hyperthyroidism with diffuse enlargement of the gland. *Group 4.* Spontaneous myxedema. *Group 5.* Myxedema after surgery without exophthalmos during the course of the thyrotoxicosis. *Group 6.* Myxedema after surgery with exophthalmos during the course of the thyrotoxicosis.

static survey of a wide field, or cross section of a mass of unselected thyroid material as seen in the clinic, rather than a dynamic study of the progress of exophthalmos in selected cases. In figure 2 the heights of the columns represent the measurements of protrusion in millimeters. When the two eyes had the same degree of protrusion the measurement is represented by a column in full black. When the protrusion was asymmetric the smaller is shown in black, the larger in white.

As a normal control the eyes of 50 healthy persons were measured and the readings all fell between 14 and 17.5 millimeters. Any measurement over the latter figure is, therefore, considered to be exophthalmos. This is indicated by an arrow in figure 2.

The thyroid cases are arranged in figure 2 in groups as follows:

1. Thirteen patients with non-toxic nodular goiter, giving no past history of exophthalmos and not appearing to have it at the time of examination; five of whom had previously been operated upon and eight others who had no operation. The measurements ran from 14 to 18 millimeters. Only one was above the higher range of normal.

2. Three patients with toxic nodular goiter, two of whom gave the history of exophthalmos in the past and appeared to have it at time of examination, and one with no such history or appearance. Their measurements ran from 15 to 22 millimeters; one normal, two exophthalmic.

3. Fifty-eight thyrotoxic patients with diffuse goiters, 40 of whom gave a history of exophthalmos, and all of whom appeared to have it at the time of examination. Their measurements ran from 18 to 25 millimeters. That is to say, all were above normal.

4. Thirty-four cases of spontaneous myxedema, all of whom had ceased taking thyroid for at least a week. The one showing the greatest protrusion had never had thyroid therapy. None of this group gave a history of exophthalmos, nor did any of them appear exophthalmic on inspection, but the actual measurements of their eyes ran from 15 to 25 millimeters; 21 of them, in fact, had definite exophthalmos by measure.

5. Four cases of myxedema following thyroidectomies for toxic goiter without exophthalmos. Their eye measurements were all within normal limits.

6. Fourteen cases of myxedema following thyroidectomy for toxic goiter with exophthalmos. All 14 showed exophthalmos at time of measurement, from 19 to 27 millimeters.

The largest measurement obtained, 27 millimeters, fell in this group.

The group of thyrotoxicosis and diffuse goiter (classic Graves' disease), group 3 in figure 2, was next broken down to discover the effect of time elapsing since the patient had the disease, the effect of iodine alone in treatment, and of iodine followed by surgery or roentgen irradiation.

The subgroupings of group 3 are shown in figure 3 as follows:

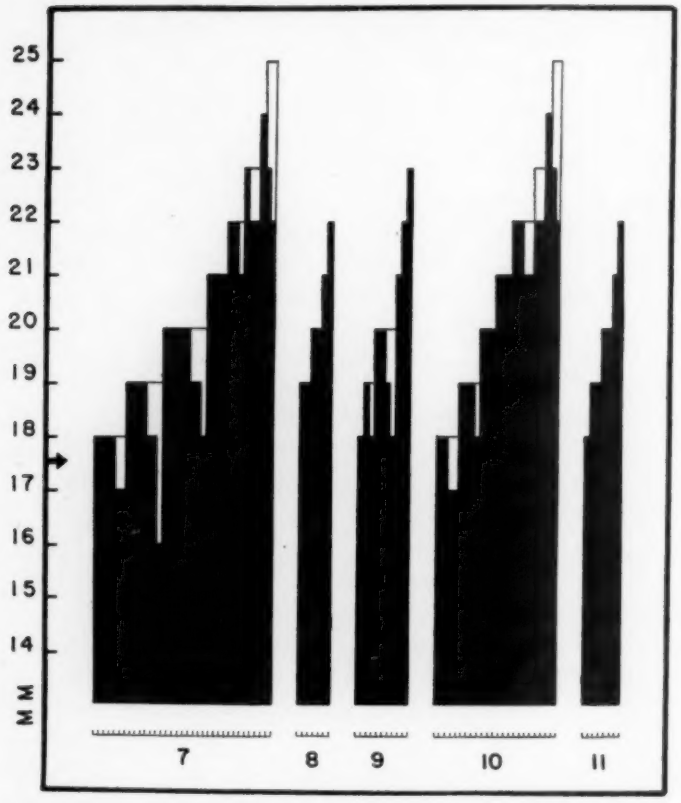

FIG. 3. Subgroup of Group 3 of figure 2 (hyperthyroidism with diffuse enlargement of the gland). *Group 7,* Thyrotoxic patients who had had the disease more than 1 year before the measurements were taken. *Group 8,* Thyrotoxic patients who had had the disease within the year when the measurements were taken. *Group 9,* Thyrotoxic patients treated with iodine alone. *Group 10,* Thyrotoxic patients treated with iodine followed by surgery or roentgen-ray treatment. *Group 11,* Patients who had received the same treatment but who had had the disease within the year when the measurements were taken.

7. Thirty-four patients who had the disease more than one year before the measurements were made. Their measurements ran from 18 to 25 millimeters.

8. Six patients who had had the disease less than one year before the measurements were made. Their measurements ran from 19 to 22 millimeters.

9. Ten patients treated by iodine alone. Their measurements ran from 18 to 23 millimeters.

10. Twenty-four patients who were treated by iodine followed by operation more than one year before the measurements were made. Their measurements ran from 18 to 25 millimeters.

11. Seven with the same treatment as group 10 but less than one year before the measurements were made. Their measurements ran from 18 to 22 millimeters.

Discussion

It appears from the results obtained that exophthalmos in Graves' disease is a condition which, when acquired, is never completely recovered from. From the present studies one cannot say that after treatment there is any change from previous conditions. It can be said, however, that in 100 per cent of those patients who were recognized as having exophthalmos during the active phase of the disease, some degree of this condition was persisting at the time thereafter when our measurements were made.

Of our 42 patients with thyrotoxicosis and exophthalmos (40 with diffuse and two with nodular glands), three had had the disease six years before the measurements were made; two had had it seven years before; one had had it eight years before; three had had it nine years before; one had had it 11 years before; three had had it 12 years before; three had had it 14 years before; two had had it 15 years before; two had had it 16 years before; one had had it 18 years before; one had had it 20 years before; and one had had it 24 years before. Even after these long periods of time patients showed measurable exophthalmos. Furthermore, as brought out in figure 3, it appears that neither duration nor type of treatment for the Graves' disease abolishes altogether the exophthalmos. Some degree of it persists if ever it has been present.

In the case of myxedema, exophthalmos was not noted clinically, but when measurements were taken it was proved to be present. It probably was not recognized on inspection because the puffiness of the surrounding tissues obscured the protrusion, and because such related eye signs as stare and lid retraction were lacking.

It may be now permissible to attempt an explanation of the findings. The weight of evidence available—clinical, anatomic, and experimental—indicates that edema of the intraorbital tissues, connective tissues and fat, as well as of the muscles, plays an important rôle in the genesis of the exophthalmos of human Graves' disease. The muscles, furthermore, in some cases, are the seat of lymphocytic infiltration and degeneration of their fibers.

Certain experimental work [2, 3, 4, 5, 6] seems to indicate that excess of thyrotropic hormone may be responsible for exophthalmos in animals. Indeed, as long ago as 1910 Gley [7] demonstrated that exophthalmos may follow thyroidectomy in rabbits and dogs, and in discussion of his paper Poncet [7] offered the interpretation that this effect might be due to overactivity of the pituitary. The inference has, therefore, been drawn that this hormone is responsible for the exophthalmos of human Graves' disease, and indeed it cannot be gainsaid that, in some cases, it may play a part. However, that it is the whole cause of exophthalmos in all cases of human Graves' disease, is most unlikely. Undoubtedly there are other factors operating as well. The theory of thyrotropic hormone causation of exophthalmos would imply that all cases of Graves' disease with exophthalmos

are due to stimulation by the pituitary, and contrariwise that those without exophthalmos are not so caused. But such is not in accord with the facts. For example, by present methods [8, 9] it cannot be shown that there is any excess of thyrotropic activity in the blood or urine of patients with classic Graves' disease. Furthermore, in acromegaly, in which an excess of thyrotropic activity can be fairly regularly demonstrated, there may or may not be exophthalmos. In the special type of Graves' disease, described in previous papers from this clinic,[1] there is an excess of thyrotropic activity in the blood and urine as in acromegaly.[9, 10]

Furthermore, it is difficult to understand how a humoral agent like a hormone which bathes all tissues could produce edema in one set of muscles and one lot of fat and connective tissue without involving other muscles, connective and fat tissue of the body.

It seems to the writer that the explanation of localized edema in a general disturbance such as thyrotoxicosis should be sought in the special anatomic characteristics of the orbit and its contents, which would make these tissues react in a different way from similar tissues in the remainder of the body.

The eyeball fits the orbit somewhat as a cork does a bottle, and it is maintained in position by the action of two pressures working in opposite directions. One of these is the pressure exerted by the tension of muscles, which tends to pull the eyeball backward; the other is the tissue pressure of the orbital contents, which tends to push the eyeball forward. The two are in such balance in health as to maintain a constant volume of orbital content, and at the same time to secure normal movement of the globes and circulation of the orbit.

That an intra-orbital tissue pressure actually exists can be proved by taking tonometric readings as is done for measuring any tissue pressure.[11] That the position of the eye is determined by the relative magnitude of the opposing pressures is indicated by the following facts. (1) In cases in which it may be inferred that tissue pressure drops, as in loss of intra-orbital fat or water from starvation or dehydration, enophthalmos develops. (2) In cases in which it may be inferred that tissue pressure rises, as in intraorbital tumors, exophthalmos develops. (3) When muscular tension is diminished as in paralysis of the ocular motor nerves, exophthalmos is produced.

The mechanism of production of edema in general has been studied by many authors, and the factors involved seem to be essentially the following:

1. Increased intracapillary pressure. This may result from either increased arterial or venous pressure.

2. Decreased osmotic pressure of the blood. This may be due mainly to low protein content.

3. Dilatation of capillaries. Hudach and McMaster[12] showed that an increased extravasation of dye occurs in the rabbit's ear when the ear is exposed to heat which causes capillary dilatation.

4. Increased capillary permeability.

5. Diminished tissue pressure in tissues traversed by capillaries. This factor produces a passage of fluid across the capillary wall until accumulation of it in the tissues causes a rise of pressure which prevents further extravasation.

Factors 1, 2, 3 and 4 can be shown to exist in thyrotoxicosis. Concerning factor 1, it is known that an increase of pulse pressure is found in this disease. Concerning factor 2, it has been shown by Brown and Mecray [13] that in 15 out of 24 thyrotoxic patients there was a serum protein level lower than that of normal persons. Also Bartels [14] got similar results in 43 cases and says, "This deviation of serum-protein content from normal may have physiological effects on the body as a whole. It may be responsible for the edema in cases of hyperthyroidism that is not caused by cardiac or renal insufficiency." In his studies Bartels shows that 63 per cent of patients had total serum protein values below the lowest level of the normal range and the serum albumin content was below normal in 73 per cent of the cases.

Concerning factor 3, Roberts and Griffith,[15] studying the cutaneous capillaries in thyrotoxic patients, showed that "most of the cutaneous capillaries are open."

Concerning factor 4, White and Jones [16] have shown that patients with thyrotoxicosis tend to have rates of filtration from capillaries in the upper range of normal. Of this finding they say, "Wide dilatation of the capillary bed produces an increase in the available surface of capillary endothelium."

Bartlett [17] states that in hyperthyroidism there is a tendency to water retention which causes pulmonary and cerebral edema in some cases. He also considers that the "arteriolarization" of the venous blood, demonstrated by Gladstone [18] in such cases, is a collateral factor in the production of edema.

From all these facts it seems probable that in hyperthyroidism there is a tendency to the production of edema. We may say, perhaps, that while at a thyrotoxic level the organism is being maintained at the upper limit of its water regulating capacity, gross edema does not occur because of the diuretic action of thyroid hormone present in excess. When thyrotoxicosis is abolished, however, as by thyroidectomy, there is a rapid retention of water due to the cessation of diuretic action of thyroid hormone, while the water retaining factors are still in action; included among these may be an unopposed action of thyrotropic hormone.

The explanation of edema in the orbit may be found in the simultaneous action of the edematogenic factors already mentioned, on the one hand, and to decreased pressure of orbital tissues upon their capillaries, on the other hand. This decrease in tissue pressure may be brought about through relaxation of the extra-ocular muscles, occasioned by the weakness which

besets them in thyrotoxicosis, along with other muscles of the body. It is well known that a more or less generalized myasthenia is a feature of thyrotoxicosis. In this myasthenia the extra-ocular muscles are probably involved. Several signs of myasthenia may be apparent. Often only muscular weakness, but in extreme cases actual atrophy may be evident.[19] The process may involve the eye muscles so as to produce a genuine exophthalmic ophthalmoplegia.[20] The frequent sign of poor convergence may be taken to be evidence of participation of the eye muscles in the general myasthenia. Adler [21] found that 24 of our 33 thyrotoxic persons showed positive reactions for myasthenia gravis.

The extrinsic muscles of the eye differ from others in that one point of their insertion is attached to bone and the other to a freely movable object, the eyeball. Weakness or paralysis of these muscles will permit the eyeball to move forward, due to unopposed intra-orbital tissue pressure. For example, Dixon [22] says, " Proptosis (unilateral) may also result from paralysis of the external ocular muscles. This is seen in some cases of myasthenia gravis—though as a rule the proptosis in this condition is bilateral. . . . The increased degree of force necessary to replace the eye in the first and subsequent examinations must be due to an increase in the fluid content of the orbit." And among other patients he describes two with unilateral exophthalmos, probably due to thyrotoxicosis with palsy of the third, fourth and sixth nerves and one due to early progressive muscular atrophy with palsy of the third and fourth.

As has been said above, it is the tension of the extra-ocular muscles which maintains the pressure inside the orbit. Relaxation of the muscles causes a diminution in tissue pressure and, as a result of this diminution in pressure, all of the five edematogenic factors enumerated above are present simultaneously in the orbit. These are increased capillary pressure, decreased osmotic pressure, capillary dilation, probably increased capillary permeability—these being local manifestations of a generalized process—and in addition drop in orbital tissue pressure which is the result of the local starvation of the orbit.

As a result of the excess of fluid that had passed from the capillaries to the tissues, the pressure rises and prevents further extravasation of fluid. At this moment an equilibrium of tensions and pressures within the orbit will again have been achieved, but with this difference from the normal state, that the contents of the orbit will have increased in volume owing to the extra fluid added to it, and the eyeball will be occupying a more forward position.

When these events have occurred, other changes may take place in the orbit, if the edema be considerable. The muscles may degenerate and become infiltrated with lymphocytes. An obstacle to venous return, from pressure of edema on veins, may develop, which can aggravate the picture and produce the type of progressive exophthalmos with marked edema of the eyelids and edema and injection of the conjunctivae.

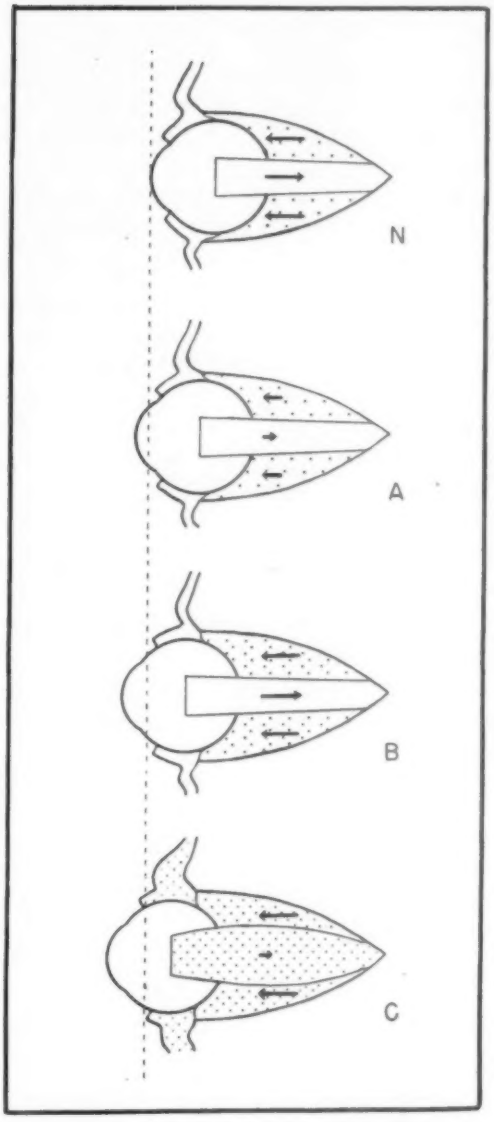

FIG. 4. Schemata representing the mechanism involved in the production of exophthalmos. The lids, the eyeball, one muscle and the intra-orbital tissue are represented. The arrows indicate the direction of pressures and tensions. The dots represent the amount of fluid in the tissues. In Schema N is shown the situation in health. The pull of the muscle is of the same magnitude as the tissue pressure and balances it, so that the position of the globe is that found in normal persons, indicated in these schemata by the interrupted line. Schema A shows the first step in the development of exophthalmos. The muscle has weakened, exerts less tension, indicated by the shortened arrow. The tissue pressure therefore forces the eyeball forward. As this happens tissue pressure falls and fluid passes from capillaries to tissue to occupy the space, until a new equilibrium is reached with the muscles stretched and the eyeball protruding.—Schema B. In Schema C is shown the situation in progressive exophthalmos in which a weakened and degenerate muscle cannot withstand the tissue pressure and in its turn becomes edematous as do the lids and surrounding tissues.

The magnitude of the various factors will determine the degree of exophthalmos. Soley [23] has shown that exophthalmos progresses after operation in a considerable percentage of the cases. This can be ascribed to a retention of water during the postoperative period. Some of the most severe cases of exophthalmos appear in patients who have had generalized edema during the course of the disease. Certain of the patients seen in the Thyroid Clinic of the Massachusetts General Hospital have shown improvement in their exophthalmos under the influence of restricted fluid and salt, and the administration of diuretics. There was improvement but no complete cure. The eyes did not return to a totally normal position. Long-standing edema can produce irreversible changes in the form of fibrosis—compare, for example, the brawny edema of the legs in chronic heart disease, from which total recovery would be impossible. Also, if we consider that the extra-ocular muscles are themselves edematous, infiltrated and degenerated, it is easy to understand their incapacity ever to return to their normal length, which would be necessary to the complete evacuation of extra water from the orbit.

The explanation of exophthalmos in spontaneous myxedema may be similar, namely that such patients retain water unduly, and also have weak muscles. Other diseases in which there is water retention may be accompanied by exophthalmos, as chronic nephritis [24] or hypertension, or in experimental chronic renal insufficiency as shown by Marine.[25]

The exophthalmos produced in myxedematous animals by injections of thyrotropic hormone may be explained on the same basis, namely that this hormone through its water-storing action aggravates the edema already present. In the intact organism, the thyrotropic hormone may lead to exophthalmos by two mechanisms, one producing hyperthyroidism and the other causing water retention. The impossibility of producing exophthalmos by the administration of thyroid in the normal animal can be explained by loss of fat and dehydration of the orbit. As a matter of fact enophthalmos can take place in animals which have lost weight rapidly and intensely, and exophthalmic animals can be benefited by the injection of thyroxin as well as by starvation or dehydration.

Summary

In this paper are presented measurements of the degree of protrusion of the eyes in 126 patients seen in the Thyroid Clinic, 13 of whom had nontoxic nodular goiters, 3 had thyrotoxicosis with nodular goiter, 58 had thyrotoxicosis with diffuse goiter, 18 had myxedema following surgery to the thyroid and 34 had spontaneous myxedema.

Exophthalmometric measurements were made with a modified Luedde exophthalmometer. For control the eyes of 50 normal persons were measured. The upper limit of protrusion in these normals was found to be 17.5

millimeters. Therefore in patients any measurement greater than this was considered to be exophthalmos.

In all of those patients who had been recognized to have had exophthalmos during the active phase of their disease, some degree of it was persisting at the time thereafter when measurements were made.

Patients who had no history of exophthalmos during the course of their disease gave measurements within normal limits when examined by the author.

The usual forms of treatment for Graves' disease, whether iodine alone or followed by surgery or roentgen irradiation, seem incapable of completely abolishing exophthalmos.

Of 34 patients with spontaneous myxedema, 21 had exophthalmos by measure.

The thyrotropic hormone is considered not the sole factor in the production of exophthalmos, but rather one among several.

There are some reasons for supposing that in thyrotoxicosis there is a tendency toward the production of edema, and that the organism is maintained at the upper limit of its water regulating capacity. Gross edema may not occur because of the diuretic action of thyroid hormone in excess.

In the production of edema in the orbit, it is believed that the extraocular muscles play an important rôle. Under conditions of health they, through the tension they exert, maintain a certain intra-orbital tissue pressure which is necessary to normal circulation in the orbit. In thyrotoxicosis, due to the weakness of the muscles which accompanies it, there is a drop in orbital tissue pressure which permits the escape of fluid from the vessels. This state of affairs also is aggravated by other edematogenic factors which are present, namely, increased pulse pressure, decreased osmotic pressure, dilatation of capillaries and increased capillary permeability.

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DIGITALIS IN THE PREVENTION OF RECURRENT CARDIAC FAILURE IN PATIENTS WITH SINUS RHYTHM *

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Although digitalis is one of the oldest drugs used in specific cardiac therapy, and probably the most widely used, there is still some dispute as to its indications and value under various circumstances. Opinions range from those recommending that digitalis be administered in all cases of heart disease (Christian,[1] Cloetta [2]) to those stating that digitalis has striking value only in cases of auricular fibrillation, and here only by slowing the ventricular rate (Lewis [3]). That digitalis slows the ventricular rate in auricular fibrillation has been conclusively demonstrated (Mackenzie,[5] Cushny [4]). This may improve the efficiency of the heart and produce striking relief of symptoms. In patients with sinus rhythm, however, some still question the indications for digitalis administration (Lewis,[6] Cotton [7]). Recent observations indicate that this drug is effective in relieving congestive heart failure in a certain percentage of patients with sinus rhythm (Pratt,[8] Christian,[9] Luten,[10] Marvin,[11] Harrison, Calhoun, and Turley,[12] and Gravey and Parkinson [13]).

We have been interested in a different aspect of this problem, viz., whether digitalis will, in an ambulatory patient who has recovered from cardiac failure, prevent a recurrence of the failure. Gold and DeGraff [14] have shown that in auricular fibrillation digitalis must be continuously maintained to prevent recurrences of the failure. In these cases it may operate in part at least by preventing excessive elevation of the ventricular rate under the diurnal stresses which the patient may encounter, as shown by Weinstein, Plaut and Katz.[15] Many textbooks (Harrison,[16] Fishberg,[17] White,[18] Luten [19]) carry the statement, admittedly empirical, that digitalis should be of value in preventing cardiac failure in patients with regular rhythm. This is in accordance with widespread clinical opinion. We are not aware, however, that any objective data have been presented in support of this concept. It is this concept that we have attempted to study in an objective manner.

Methods

Four patients who had previously shown cardiac failure with a regular rhythm and who had regained compensation on the usual therapy (bed rest,

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fluid restriction, salt restriction, diuretics, and digitalis) were under observation for a period varying from 31 to 60 weeks. Three patients had hypertensive heart disease and the fourth had arteriosclerotic heart disease. All were ambulatory throughout the period of study (with one exception who during a period of failure was hospitalized), and were kept on a comparable régime of activity, salt, fluid and caloric intake; the only controlled variable was the administration or omission of digitalis, and, when advisable to relieve heart failure, the intravenous administration of a mercurial diuretic. The powdered leaf was the preparation used. No fixed dosage was employed, the drug being given so that digitalization was accomplished in a week; this usually required 0.3 gm. daily for seven days. The dose was then maintained at a level of 0.1 to 0.2 gm. daily. After a control period of observation on maintenance dosage, the digitalis was omitted and the patient observed for subjective and objective evidence of cardiac failure. Upon the appearance of heart failure the patient was treated with whatever measures were necessary to restore compensation, after which the same routine was repeated. The period of intensive therapy to alleviate well-marked congestive failure never extended over more than two weeks, and was always followed by a suitable control period on digitalis alone before this drug was again omitted. Two periods of withdrawal of the drug were observed in two patients and three periods in the other two patients. Patients were excluded from the study who during the course of observation failed to report regularly, were unreliable, or developed conditions known to precipitate cardiac failure (acute infections, myocardial infarction, pulmonary infarction, thyrotoxicosis, etc.). No case was excluded because of inconsistency of response to digitalis withdrawal.

The patients were seen fortnightly as a rule, and were questioned and examined for clinical evidences of heart failure. In addition to this the following objective tests of circulatory status were performed on each visit under comparable conditions after a preliminary rest period: vital capacity, venous pressure, response of venous pressure to compression of the right upper quadrant of the abdomen, and circulation time. The vital capacity was determined in the sitting position, using a McKesson-Scott bellows type of instrument which was checked against a water spirometer. The best of three efforts was taken as the correct reading. Venous pressure was determined by the direct method, using a simple instrument which we constructed ourselves. This consists of a Kaufman-Luer syringe to the sidearm of which a 35 cm. length of glass tubing of similar diameter and bore was connected by means of a 1-inch piece of rigid rubber tubing, producing in effect a 36 cm. sidearm. This sidearm was completely filled with sterile 3 per cent sodium citrate solution, an 18-gauge needle inserted into an antecubital vein, and the plunger withdrawn until just beyond the orifice of the sidearm. The citrate solution in the tube was allowed to drop until it reached a stationary level. Ten centimeters above the table top was taken as the zero

level (Lyons, Kennedy and Burwell [20]), and the difference between these two levels was read as the venous pressure. In every case we also noted the effect on the venous pressure of compression of the right upper quadrant of the abdomen for one minute (Oppenheimer and Hitzig [21]). Using the same needle, 3 to 5 c.c. of a 20 per cent calcium gluconate solution * were injected as rapidly as possible, the time of injection averaging approximately 1.4 seconds. The time from the beginning of injection until the first appearance of a sensation of warmth in the mouth or throat was recorded by a stopwatch. This test was always repeated 60 seconds after all sensation of warmth had disappeared, and the average of the two tests taken as the arm-to-tongue circulation time. In each patient the amount of solution injected was always the same. The patients were weighed at each visit under comparable conditions. The resting pulse and respiration were recorded on all visits, and the immediate and delayed (two minutes) effect of a standard exercise, which consisted of 10 round trips on a three-step platform, was observed.

Results

Our results are shown in chart form in figures 1 to 4. Vital capacity determinations were not followed in one patient (P. B.) because this patient, although very coöperative, could not seem to master the technic required for this test. The venous pressure is expressed in centimeters of water. Rise on right upper quadrant pressure represents the increment when this maneuver was performed, and is expressed in millimeters of water. In no patient did we find any consistent significant variations in the respiratory rate, which we have, accordingly, omitted from the graphs. As a rule, we found variable correlation in the pulse rate, both resting and on standard exercise. These changes have been indicated in the case of one patient (figure 1), and in the other three similar results were obtained. The solid line connects the resting pulse rates at the various visits. The broken lines at each visit represent the pulse rate immediately after and two minutes after the standard exercise. The degree of failure represents our clinical estimation of this status on each visit, using 0 as the absence of all signs and symptoms and ++++ as the most severe degree of failure. The solid bars at the top of the figures indicate the period during which digitalis was being withheld. The remainder of the figures are self-explanatory.

Patient 1 (R. C.), whose chief symptom was dyspnea on exertion, reported aggravation of this symptom upon withdrawal of digitalis. This was manifested objectively in a very decisive manner by a reduction in his vital capacity (figure 1), and at a later stage and to a lesser degree by the appearance of basal râles. His circulation time also tended to become prolonged during these periods, but varied in a less consistent manner than did his vital capacity. His venous pressure showed very little variation. However, a rise in venous pressure on right upper quadrant compression did appear upon withdrawal of the drug; this phenomenon tended to precede or

* Kindly supplied by Sandoz Co.

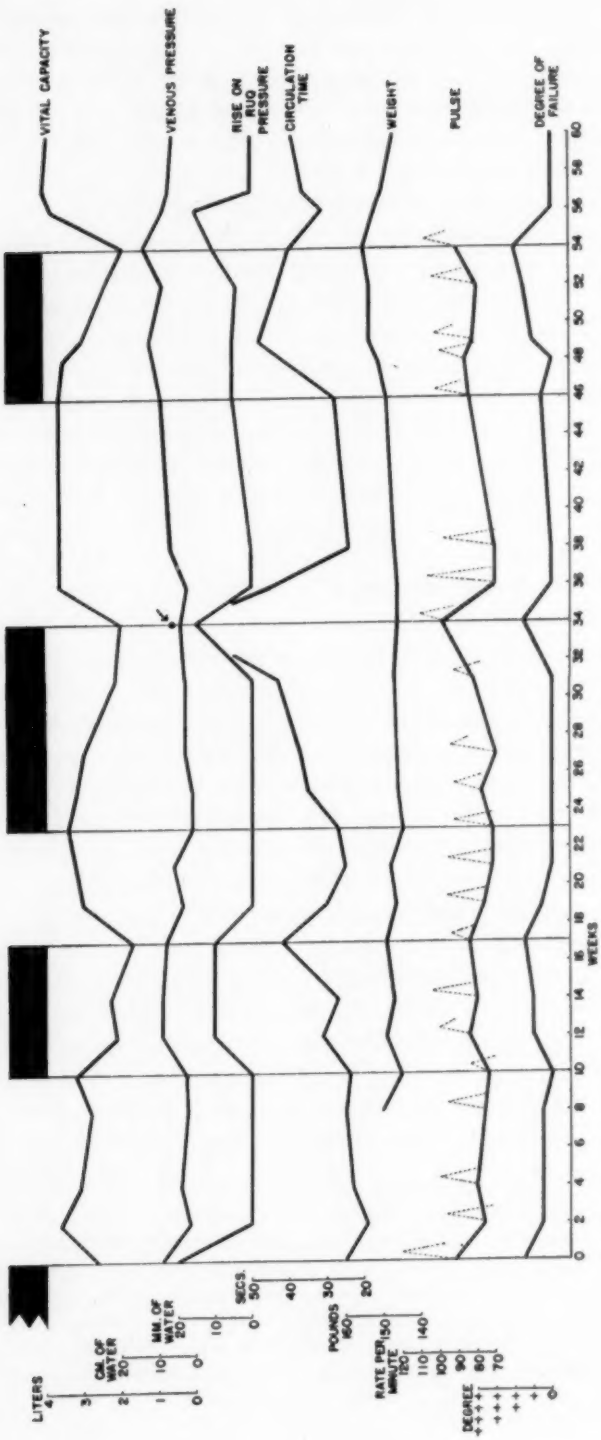
VITAL CAPACITY
VENOUS PRESSURE
RISE ON RUQ PRESSURE
CIRCULATION TIME
WEIGHT
PULSE
DEGREE OF FAILURE
WEEKS
LITERS
CM. OF WATER
MM. OF WATER
SECS.
POUNDS
RATE PER MINUTE
DEGREE

FIG. 1.

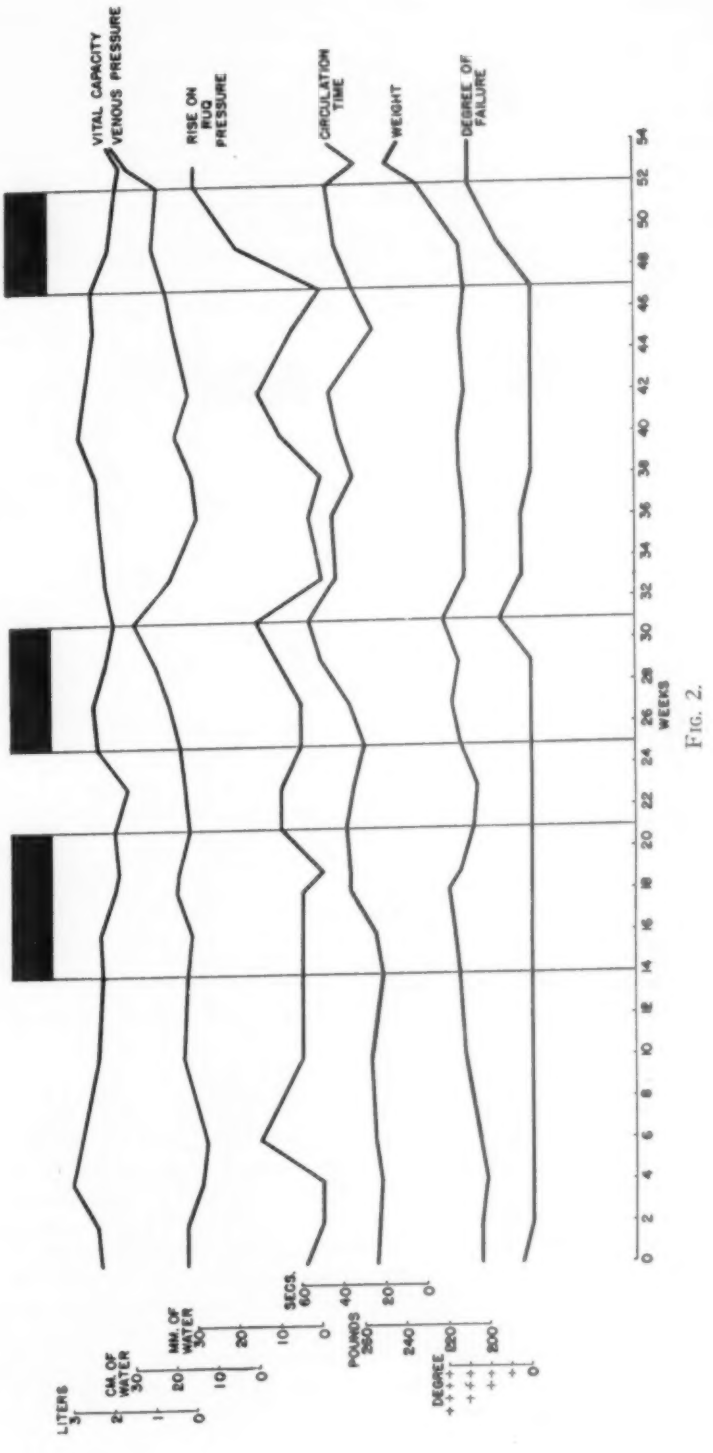
VITAL CAPACITY
VENOUS PRESSURE
RISE ON
RUG
PRESSURE
CIRCULATION
TIME
WEIGHT
DEGREE OF
FAILURE
WEEKS
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 54
LITERS
5
2
0
CM. OF
WATER
30
20
10
0
MM. OF
WATER
30
20
10
0
SECS.
60
40
20
0
POUNDS
260
240
220
200
DEGREE
++++
+++
++
+
0

FIG. 2.

coincide with clinical evidence of liver engorgement. Neither the resting pulse rate nor the response of pulse to standard exercise showed a consistency of response to which we could attach any value. We found this latter to be true in all of our cases, and have, therefore, omitted it in the other three charts.

In patient 2 (H. M.) no single procedure mirrored his changing circulatory status as remarkably as did the vital capacity in the first patient (figure 2). During his first period of digitalis withdrawal, the vital capacity was decreased and the circulation time prolonged, but there was no significant change in venous pressure nor did clinically observable signs of cardiac failure appear. During the second period of withdrawal all observations changed concurrently, and definite congestive failure appeared. During the third period all observations showed a trend in the same direction, the most marked change occurring in the response of venous pressure to right

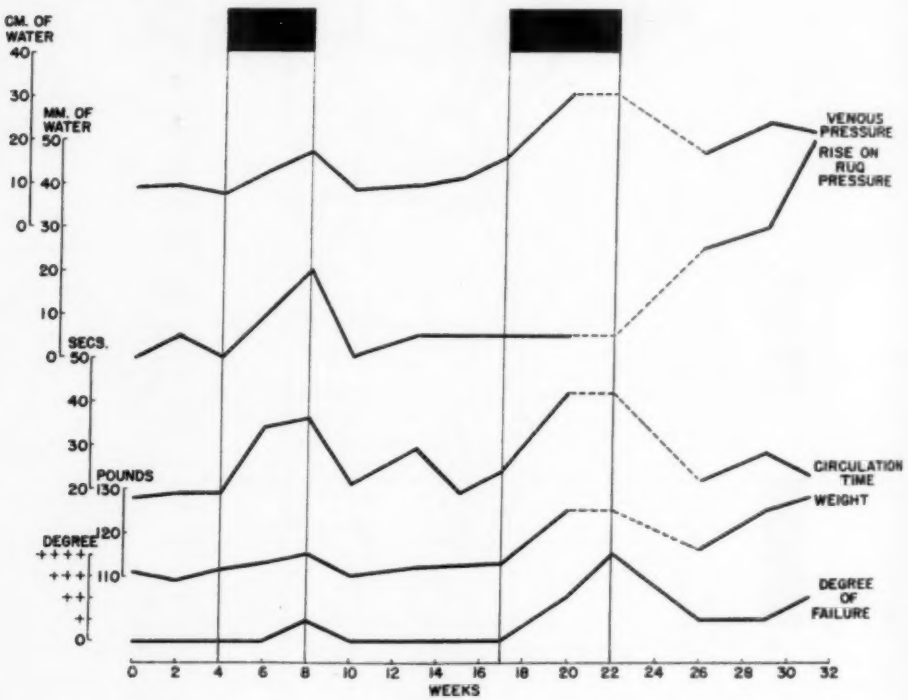

FIG. 3.

upper quadrant compression. After this time digitalis, as well as all other therapy, was of no avail, the patient dying in the hospital in severe congestive failure.

Patient 3 (P. B) was followed through two periods of digitalis omission. During the first, clinical signs of failure of a slight degree developed, but the venous pressure and especially the circulation time showed earlier and more marked changes (figure 3). During the second, definite changes occurred in venous pressure, circulation time, and clinical status. It was on this occasion that hospitalization became necessary. Cardiac compensation was not completely restored and this patient thereafter developed progressive cardiac failure despite digitalis administration. Later, even though she was hospitalized and given intensive therapy, she died in the hospital 38 weeks after the beginning of the study. Her weight tended to correspond with the degree of clinical

failure, probably more nearly so than did any other observation. It is noteworthy that after her second period of digitalis withdrawal, her circulation times were not elevated to a degree corresponding to her venous pressure, clinical signs and weight. On her last out-patient visit, when the venous pressure was 22 cm. and rose 50 mm. on right upper quadrant pressure, the circulation time was only 23 seconds, a reading which was checked three times because of the apparent inconsistency, all three readings being within the range of 22 to 24 seconds.

Patient 4 (R. T.) went out of town twice during the study. In each instance he was taking digitalis when he left, and continued to do so until his supply ran out. He returned to the out-patient department, once three weeks after and once four days after discontinuing the drug, and on each occasion reported that he had felt perfectly well

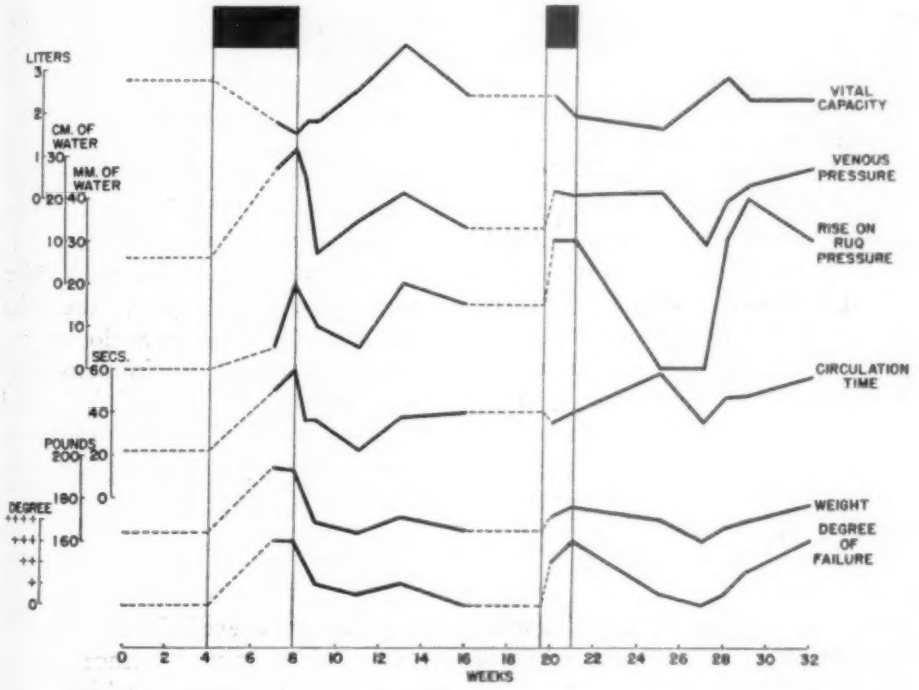

FIG. 4.

until he stopped the digitalis. In his case the vital capacity, venous pressure, circulation time, weight, and clinical degree of failure all tended to run roughly parallel (figure 4). However, some discrepancies among the various observations were noted between the twenty-fourth and twenty-eighth weeks of the study. At this same time his cardiac reserve had become so diminished that failure progressed in spite of full digitalization. Shortly after the completion of the study this patient entered the hospital, where his condition could not be improved beyond Class IV functional capacity (New York Heart Association [22]).

In treating the congestive failure which followed the third period of digitalis withdrawal in H. M. (figure 2), the second in P. B. (figure 3), and both first and second in R. T. (figure 4) mercurial diuretics were used in addition to digitalis. The maximum quantity used was 4 c.c. over a period of two weeks.

Discussion

In every instance signs of cardiac failure appeared following withdrawal of digitalis. The consistency of this occurrence indicates that the relationship is one of cause and effect, and not that of coincidence. The evidence herein presented offers strong objective support to the current impression that digitalis is of value in the prevention of recurrent cardiac failure in patients with sinus rhythm. We found, however, that as the cardiac reserve of a patient diminished, a stage was finally reached (patients 2, 3, 4) where digitalis was no longer effective in preventing the development of congestive failure. The serious outcome when this supervened—two patients died, and the third is left in an irreversible Class IV functional capacity—suggests, even from such a small series, that when a patient who previously responded fails to respond to digitalis therapy, the prognosis is grave. One must, of course, eliminate infections, thyrotoxicosis, etc., which diminish responsiveness to digitalis.

Although not the direct object of the study, our data suggest that digitalis also has value in restoring compensation in patients with sinus rhythm when cardiac failure had occurred. Thus, in six of the ten instances in which signs of failure developed upon digitalis withdrawal the resumption of digitalis administration produced a recession of these signs to the point of restoration of compensation. The four remaining instances do not negate this finding, because the mercurial diuretics were started simultaneously with the digitalis, and were not given as a final resort after digitalis had been tried alone. We administered both together at these times because we deemed it advisable to alleviate the patients' congestive failure as speedily as possible. Our evidence regarding the efficacy of digitalis in alleviating congestive heart failure in patients with sinus rhythm conforms to that presented by other investigators, [8, 9, 10, 11, 12, 13] adding only the concept that this action may be produced in ambulatory patients. We must point out, however, that in those instances in which digitalis alone relieved the cardiac failure, the latter was of relatively mild degree. We have no evidence regarding the comparative value of digitalis relative to other measures which might have been used, nor do we have evidence that digitalis alone can alleviate a *severe* degree of congestive failure in these ambulatory patients.

We did not attempt to study the mode of action of digitalis. This is itself a disputed question (Harrison,[16] Peters and Visscher,[23] Katz et al.,[24] Stewart et al.,[25] Gold and Cattell [26]). Nothing in our data casts any light upon this problem, and our results are compatible with the opinions of any of these investigators.

The repeated fortnightly observations over a period of months, as the patients were developing and recovering from cardiac failure, offered an excellent opportunity to evaluate the various circulatory tests employed. Our experience indicates that no single test was uniformly consistent in reflecting the earliest circulatory changes, although the combined data proved

satisfactory in following the changes in circulatory status. The response of venous pressure to right upper quadrant compression showed changes in patient 1 in the absence of marked changes in the venous pressure itself, but at times in the other patients its results were at variance with those of the other tests. In patient 3 it is notable that the circulation time in the latter weeks showed relatively little change in comparison with the other findings indicating failure of the heart. In patient 1 the reverse is true, the circulation time being prolonged in the latter weeks out of proportion to the other findings. The discrepancy in time relationship of the changes occurring between the twenty-fifth and twenty-eighth weeks in patient 4 has also been previously mentioned. We heartily recommend the use of these various tests in studies of this type in which objective data which can be presented and evaluated are desired, and a trend rather than a single determination is sought. In routine clinical practice, however, their value should be more limited because only seldom does one gain information from them that cannot be obtained from careful anamnesis and examination of the patient. Nor would we advise that the status of the circulatory system be judged by the results of any one of the tests at any one time—in our hands, at least, the results have not proved sufficiently reliable. The various tests which we have used require training in their performance and are just as subject to personal interpretation as is the simple clinical examination. When used, they should be correlated with all other available data. Each of these tests is subject to other variations in cardiovascular dynamics besides heart failure, and hence cannot be used as a sole measure of the presence or degree of heart failure. Nevertheless, our assembled data show clearly that a trend toward congestive failure occurred each time digitalis was withdrawn.

A complication such as acute infection, myocardial infarction, thyrotoxicosis, etc., may precipitate heart failure in a patient whose cardiac reserve has previously been unimpaired. It is also possible that recovery from such an episode may be so complete that the cardiac status may return approximately to its previous level. All of our patients, however, had developed congestive failure in the natural course of their disease, indicating that the reserve of their hearts had become markedly diminished. It does not follow from the evidence we obtained that digitalis should prove of prophylactic value in patients with little reduction in cardiac reserve; the objective procedure used in this study is not suitable to determine the value of digitalis in patients in whom cardiac failure is not so imminent. The use of this drug in the latter type of patient is still a matter of empirical judgment.

Summary and Conclusions

1. Four ambulatory patients with sinus rhythm, who had previously shown congestive heart failure, were studied for periods varying from 31 to 60 weeks. Each was kept on a comparable controlled régime of activity,

salt, fluid, and caloric intake. The only variable was the administration or omission of digitalis.

2. In every instance cardiac failure recurred when digitalis was withdrawn. We conclude, therefore, that the administration of digitalis tends to prevent the development of failure in patients with sinus rhythm. Digitalis also proved to be of value in relieving the congestive failure produced in these ambulatory patients by withdrawal of this drug.

3. In three patients the cardiac reserve finally became so diminished that irreversible cardiac failure occurred in spite of all therapy.

4. The objective measurements of vital capacity, venous pressure, response of venous pressure to right upper quadrant compression, circulation time, and weight, when correlated with the clinical findings, proved to be of value in following the trend of the circulatory status.

5. Continuous digitalization is of value in preventing recurrences of cardiac failure in ambulatory patients with sinus rhythm. It is unwise to omit this drug in patients with diminished cardiac reserve who have previously shown failure, even though the patient is free of symptoms.

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GAUCHER'S DISEASE *

I. A CASE WITH HEMOLYTIC ANEMIA AND MARKED THROMBOPENIA; IMPROVEMENT AFTER REMOVAL OF SPLEEN WEIGHING 6822 GRAMS

By Harry Mandelbaum, M.D., F.A.C.P., Louis Berger, M.D., F.A.C.S., and Max Lederer, M.D., *Brooklyn, New York*

II. LIPID ANALYSIS OF THE GAUCHER'S SPLEEN

By Albert Edward Sobel, B.S., Ch.E., A.M., Ph.D., and Irving Allan Kaye, B.A., M.Sc., *Brooklyn*

Part I. A Case with Hemolytic Anemia and Marked Thrombopenia

The subject of Gaucher's disease continues to occupy a fairly prominent position in the medical literature of recent years. The disease is not rare, although the total number of cases reported is not large. The following case is of special interest, first, because it is another instance of Gaucher's disease recognized in the fifth decade; second, because of the presence of an active hemolytic anemia necessitating recourse to splenectomy. The spleen removed is the second largest ever to be reported, and probably the largest specimen that ever taxed the skill of a surgeon.

Case Report

First Admission. J. H., 39 years of age, first entered the Jewish Hospital on April 13, 1936. His family history was entirely negative. His past history revealed that he had had typhoid fever in 1921; he had been told then that his spleen was enlarged. In 1927, he was operated on for acute appendicitis; the surgeon then noted that the spleen reached almost to the umbilicus. Since 1932, he had suffered from recurrent attacks of weakness due to anemia, with apparent improvement following the use of iron and liver preparations. In 1934, he developed ragweed hay fever; attacks had recurred annually since then. In 1934 an ulcer formed on the inner aspect of the left leg at the junction of the lower and middle thirds; it had not healed up to the time of admission.

He entered the hospital because of weakness, pallor and soreness in the left leg. Weakness and fatigability had been manifest for a few weeks, and of late, shortness of breath had attended moderate physical effort. He had noted an increasing pallor and thought he was somewhat jaundiced. He was positive in the assertion that the girth of his abdomen had steadily increased during the preceding two years.

On admission, the temperature was 100.2° F. and the pulse rate was 86 per minute. The blood pressure was 128 systolic and 66 diastolic. The patient's ap-

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From The Jewish Hospital of Brooklyn, N. Y.

pearance was striking; the skull was oxycephalic (tower-skull); the torso was barrel-shaped with its greatest diameter at the level of the sixth to the ninth ribs, and the arms, legs and face appeared thin and atrophied. The sclerae were not icteric. Irregular wedge-shaped pingueculae were present. The skin was pigmented by a patchy bronzing more marked on the exposed surfaces. The anterior aspect of each leg was likewise deeply pigmented, and on the left leg an irregular deep ulcer, 5 cm. in diameter, was noted 15 cm. above the ankle. The spleen, smooth and hard, extended on the right to the midclavicular line and below to an inch above the pelvic brim; the liver was not palpable.

Laboratory Data: Blood study: erythrocytes, 2,800,000 per cu. mm.; hemoglobin, 49 per cent (Dare); leukocytes, 8,200 per cu. mm.; polymorphonuclear neutrophiles, 45 per cent; small lymphocytes, 53 per cent; monocytes, 2 per cent; moderate anisocytosis and poikilocytosis. An occasional microcyte was noted which appeared spherical in wet preparations. Reticulocytes, 3 per cent; coagulation time, 5 minutes; bleeding time, 2½ minutes. The fragility test showed:

	Patient			Control	
	Washed	Unwashed	Cells	Washed	Unwashed
Hemolysis begins	0.44	0.46		0.44	0.44
Hemolysis complete	0.32	0.32		0.33	0.34

Chemical examination of the blood: sugar, 109 mg. per cent; urea nitrogen, 21.8 mg. per cent; creatinine, 1.3 mg. per cent. The cholesterol was low (102 mg. per cent). The icterus index was 9; the Van den Bergh, direct, delayed positive; indirect, 1.75 units. The urine contained no bile; urobilinogen was present in normal amounts.

He received a high caloric-high vitamin diet, liver parenterally and iron by mouth. A diagnosis of hemolytic anemia was made; the etiology was not established. Congenital hemolytic jaundice and Gaucher's disease were considered as possible causes. He left the hospital feeling stronger. The soreness of his left leg had abated but the ulcer had not improved. Parenteral liver injections were continued once weekly for four months; the hemoglobin was raised to 84 per cent and the red blood cell count to 4,100,000 per cu. mm.

In October 1938, in spite of careful adherence to diet and medication (liver and iron), he again complained of increasing weakness, pallor and shortness of breath. The spleen filled most of his abdomen, extending to just beyond the mid-clavicular line on the right and dipping into the brim of the pelvis below. The liver was not palpable. He was seen in consultation with Dr. Nathan Rosenthal on October 26, 1938; the hemoglobin was 51 per cent (Dare); the erythrocytes, 4,400,000 per cu. mm. The leukocytes were 24,200; the platelets, 70,000; polymorphonuclear neutrophiles, 53 per cent; eosinophiles, 1 per cent; lymphocytes, 41 per cent; monocytes, 5 per cent; reticulocytes, 5 per cent. An occasional microspherocyte was seen. The icterus index was 10. Bone marrow smears taken from the sternum on two occasions failed to show Gaucher cells; there was a marked preponderance of normoblastic elements; the myelograms were characteristic of hemolytic anemia.

Second Admission. The patient reëntered the hospital November 17, 1938, a year and a half after his first admission. His complaints were essentially the same; the ulcer on his left leg had not healed. He appeared weaker and more emaciated. The pigmentation was deeper, a slight icteric tint was noted in the sclerae and the pingueculae were more prominent. The anemia was marked. A loud systolic murmur was heard over the mitral and pulmonic areas. The lungs were clear. The spleen occupied most of the abdomen. The liver could not be felt. The pigmentation of both legs was deeper and extended to just below the knees. The ulcer on the left leg measured 3 cm. in diameter and ½ cm. in depth.

Laboratory Data: Blood study: erythrocytes, 2,600,000 per cu. mm.; hemoglobin 40 per cent (Dare); leukocytes, 11,000; polymorphonuclear neutrophiles, 46 per cent; band forms, 5 per cent; lymphocytes, 37 per cent; monocytes, 1 per cent. A few microspherocytes were again seen. The blood platelets were 20,000 per cu. mm. The fragility test showed:

	Patient		Cells	Control	
	Washed	Unwashed		Washed	Unwashed
Hemolysis begins	0.44	0.42		0.44	0.44
Hemolysis complete	0.28	0.30		0.30	0.28

Sternal puncture was done by Dr. M. Morrison; the myelograms failed to show any Gaucher cells; there was evidence of marked leukogenic and erythrogenic activity.

The Kline test with blood was negative. Chemical examination of the blood showed 89 mg. per cent of sugar and 17.3 mg. per cent of urea nitrogen. The icterus index was 17. The blood cholesterol was unusually low, 87 mg. per cent, of which 28 per cent was estimated as free cholesterol. The blood phosphorus was 3 mg. per cent and the phosphatase, 3 units per 100 c.c. The prothrombin time (Howell's method), was 10 minutes, compared to 6 minutes for the control. Renal tests showed normal function, the urine contained no bile, and urobilinogen was present in normal amounts in the urine.

An adrenalin test was done to test the contractability of the spleen. The result is recorded in table 1.

TABLE I

Time	Hgb. (Dare)	Erythrocytes Millions per cu. mm.	Leukocytes per cu. mm.	PMN. %	Bands %	PME. %	Lymph. %	Mono. %
2:00	45%	2.7	11,250	64	7	2	25	2
2:10		Adrenalin chloride, 1 : 1000, m. VII, injected subcutaneously						
2:25	50%	2.75	12,750	52	4	0	40	4
2:40	50%	2.75	20,900	33	0	0	65	2
2:55	50%	3.25	16,500	38	4	0	56	2
3:10	47%	3.05	13,600	48	4	2	42	4
3:40	47%	3.25	13,850	66	4	0	30	0
4:10	52%	2.83	12,900	62	0	2	34	2

The maximum contraction of the spleen occurred at 2:35 (25 minutes after the injection of adrenalin). The transverse diameter of the spleen, measured at its widest portion, was reduced 8½ cm.

Roentgenograms of the heart and lungs showed nothing remarkable. The bones were carefully studied; the lower dorsal and lumbar vertebrae were normal. The humeri were negative except for slight broadening of the lower end of the shaft. No deformity of the cortex or medulla could be demonstrated. The long bones of the lower extremity were normal except for a slight increased density of the condyles of the femora and of the tibial tuberosities. A slight broadening of the lower ends of the shafts of both femurs was noted.

Impression. The degree of anemia had increased progressively during the four weeks preceding his admission; it was associated with a leukocytosis and an increased icterus index; the myelograms showed active erythrogenesis. These facts constituted evidence of an active hemolytic anemia. Was it on a basis of congenital hemolytic jaundice? The family history was negative, microspherocytes were only occasionally found and the fragility of the red blood cells was not appreciably altered. The "tower skull," the presence of a chronic ulcer on his leg and an acholuric icterus in a swarthy individual favored this concept. Gaucher's disease seemed, however, more probable;

the mottled bronze pigmentation with symmetrical brownish-black discoloration of the anterior aspect of both legs, the tremendous spleen and the thrombopenia were suggestive. However, repeated myelograms failed to show any Gaucher cells, and the roentgen-ray studies were not conclusive.

In the presence of an increasing hemolytic anemia and a marked depression of the platelets, it was agreed that splenectomy was indicated.

Splenectomy was done on November 11, 1938, by Dr. Louis Berger. Anesthesia (closed ether primarily, oxygen as indicated). Incision: a left rectus incision extending from the costal arch close to the xiphoid to within 3 inches of the inguinal ligament, about 20 inches long. The spleen occupied most of the abdomen; it extended to the right midclavicular line, reached high under the diaphragm, and below it dipped beneath the pelvic brim. Numerous adhesions were encountered. The splenic pedicle was short, the vessels were very large, each the width of a finger. The gallbladder was distended; no stones could be palpated. The liver appeared slightly enlarged but not abnormal in appearance. Considerable bleeding attended the removal of the spleen, leading to shock, which was successfully combated with a continuous venoclysis of glucose and saline solutions and a transfusion of 1000 c.c. of citrated blood.

Postoperative Course. The patient reacted well; the pulse and blood pressure were normal within 24 hours. Convalescence was uneventful and he was discharged from the hospital on December 7, 1938. Changes in the hemograms before and after splenectomy are recorded in table 2. A sternal puncture was done on December 4, 1938. Dr. Morrison again failed to find any Gaucher cells.

Chemical Studies of the Blood. On November 23, the icterus index was 16.1; the Van den Bergh direct, delayed; indirect, 1.26 units per 100 c.c. blood serum. On November 30, the icterus index was 3.4; the Van den Bergh direct, negative; the indirect, 0.35 units per 100 c.c. blood serum. Cholesterol: On November 23, total, 89 mg. per cent, 23 per cent as free; cholesterol on November 30, total, 146 mg. per cent, 40 per cent as free. On November 30, the blood calcium was 9.8 mg. per cent, the phosphorus was 5.2 mg. per cent and the phosphatase was 6.8 units per 100 c.c.

Pathological Report. (Dr. Max Lederer.) *Gross.* The spleen measured 38 by 24 by 13 cm. and weighed 6822 grams. The external surface was nodular, smooth and glistening and conformed to the original shape of a spleen. Scattered throughout were numerous firm nodules which on section appeared as irregular gray areas, up to 2 cm. in diameter and well demarcated from the surrounding tissue. The spleen was divided into lobules of different size by thin and broad gray streaks; some of these lobules projected slightly above the cut surface. Throughout there was a honeycombed appearance of the parenchyma, and spaces up to 0.3 cm. were filled with blood. The blood vessels were prominent and distended with blood. The Malpighian corpuscles could not be recognized.

Microscopic. The usual cytoarchitecture of the spleen was obscured and not readily discernible. The capsule and the trabeculae were definitely thickened. The Malpighian bodies were not evident excepting in occasional areas where they appeared as small oval masses. Throughout the preparation, the sinuses were markedly distended; many were so distended as to give an angiomatous picture; the sinuses were lined with endothelial cells. Within the distended sinuses were large cells containing one or more vesicular nuclei and abundant cytoplasm in which linear streaks could be seen. In other cells, the nuclei were placed near the periphery or were absent. These Gaucher cells varied greatly in size, and in different areas in their number as well. Small hemorrhagic foci were noted. In some areas there were foci of dense hyalinized fibrous connective tissue with scattered purple blue staining deposits (calcium). Scattered throughout the preparation were accumulations of mononuclear cells containing golden-brown granules in their cytoplasm. With the

Perl stain, iron pigment was seen lying free in the tissue as well as within these large mononuclear cells; occasionally, iron pigment in small amounts was noted within a Gaucher cell. With the Laidlaw connective tissue stain, a fine reticulation was seen traversing the preparation, forming dense masses in the trabeculae. Microchemical stains suggested the lipid in the cells to belong to the kerasin type rather than the phosphatid. Diagnosis: Splenomegaly; lipoid histiocytosis of the Gaucher type.

Lipid Analysis of the Spleen. See supplement.

Subsequent Course. He continued to improve. Three months after his operation, he returned to work for the first time in five years. The ulcer on his leg healed shortly after he left the hospital and has not recurred. At the end of six months, he weighed 208 pounds (he weighed 153 pounds when he had been discharged from the hospital); his general appearance had changed, his skin was fair, his face and extremities were well rounded, and the lower thoracic bulge was not as conspicuous. On May 25, 1940, he weighed 227 pounds; his skin was fair but the pigmentation of the legs was still evident. The blood count was normal (table 2). Roentgenograms of all the bones show no changes from those previously taken. The pingueculae had completely disappeared. He was married in June 1940.

TABLE II

Date	Hgb. (Dare) %	Erythrocytes Millions per cu. mm.	Leukocytes per cu. mm.	PMN. %	Bands %	PME. %	PMB. %	Lymph. %	Mono. %	Platelets per cu. mm.
11–17	40	2.65	11,100	47	5	0	2	37	9	20,000
11–18	47	2.78	11,500	51	3	0	0	39	7	20,000
11–21	45	2.7	11,250	52	5	0	0	41	2	55,000
11–22	Splenectomy Transfusion 100 c.c. citrated blood									
11–23	45	2.92	28,000	74	9	0	0	17	0	
11–25	59	2.95	20,000	83	0	0	0	8	9	
11–26	45	2.82	19,000	64	2	2	0	24	8	
11–28	45	2.54								
11–30	42	3.2								760,000
12–2	47	2.85								
12–6	53	2.73								
12–15	64	3.8	11,000	65	3	0	0	25	7	
12–29	82	4.3	7,400	64	2	0	0	28	6	340,000
1–15	88	4.4	7,100	67	3	0	0	29	1	310,000
2–15	91	4.7	6,400	65	2	0	0	28	5	
3–18	98	5.1	6,200	58	0	0	0	37	5	
5–14	97	5.1	6,100	62	2	0	0	32	4	240,000
6–16	97	5.2	6,900	68	3	1	1	23	4	210,000
5–25	98	5.3	5,400	61	3	2	1	29	4	

Preoperative and postoperative blood studies. Patient received a transfusion immediately following splenectomy. He had received no hematinics. Note the thrombopenia before operation.

DISCUSSION

Gaucher [7] first described the disease in 1882 as a primary epithelioma of the spleen. Mandelbaum and Downey [13] in 1916 established this condition as a metabolic disturbance. In 1924, Lieb [12] and Epstein,[5] by chemical analyses of Gaucher spleens, showed that kerasin, a cerebroside, was the most important lipoid constituent.

Gaucher's disease is regarded as a non-hereditary, congenital familial disease linked with a constitutional factor involving a disturbance in lipoid metabolism; one of the primary xanthomatoses.

A classical description of the disease was presented by Mandelbaum and Downey in 1916: "Gaucher's disease begins usually in childhood or infancy, often affects several members of a family of the same generation and is characterized by progressive increase in the size of the spleen which frequently enlarges to an enormous size, and by subsequent enlargement of the liver. A characteristic discoloration (brownish-yellow) of the skin is present, usually confined to the exposed parts of the body (the face, neck and hands) and a peculiar yellowish, wedge-shaped thickening of the conjunctivae of both sides of the cornea, is seen" (pingueculae).

Some doubt has been cast on the non-hereditary character of the disease by Anderson [1] who studied a family in which there was the possibility of transmission through an unaffected male to four of his daughters.

Gaucher's disease shows a predilection for those of the Jewish race. It occurs in females twice as often as in males. The condition is usually discovered in childhood; Horsley et al.[9] reviewed 71 cases from the literature and noted that 56 per cent of the cases had been recognized before the age of eight. Wechsler and Gustafson's patient [17] was 68 years old.

The onset is insidious. In some, constant abdominal discomfort may cause them to seek medical advice at which time a large spleen is discovered. Involvement of the bones may be heralded by pain, occasionally severe enough to resemble osteomyelitis (Capper et al.[3]). Pick [15] has described a type predominantly osseous; he reported two such cases in brothers. On roentgen-ray studies, the bones appear less opaque because of a deficiency in calcium. Occasionally, the shafts of the long bones present a picture of an apparently reduplicated cortex. Welt et al.[18] found the earliest change to be a fusiform expansion of the lower one-third of the femur (the Erlenmeyer-flask-like femur).

The splenic enlargement is the important feature of Gaucher's disease. In Pick's [15] cases, the average size for children between the ages of 5 to 14 was 1800 gm.; the average size for adults was 2700 gm.; normally the weight of the spleen ranges from 150 to 160 gm.[11] Pick [15] refers to the largest spleen he had observed as weighing 8100 gm. In the case reported by Horsley et al.,[9] the spleen weighed 5890 gm.

A diffuse or spotty pigmentation especially marked on the exposed parts is of frequent occurrence. Bloom et al.[2] emphasized the presence of symmetrical areas of pigmentation involving the anterior aspect of the legs in a number of their cases; occasionally an ulcer formed. The pigmentation is an expression of a general hemochromatosis which is constantly present in this disease. The bilateral conjunctival pingueculae are likewise evidence of the hemochromatosis; it was noted in 14 of the 89 cases reviewed by Hoffman and Makler.[8]

The blood changes, according to Pick,[15] consist first of a leukopenia which may be due to a decrease in the polymorphonuclear neutrophiles or the lymphocytes; then there follows a moderate hypochromic anemia.

Thrombocytopenia is a constant feature and may be observed early. Marked evidence of myelophthisis may eventuate due to crowding of the bone marrow by Gaucher cells. Gaucher cells have never been observed in the peripheral blood but their recognition in the bone marrow smear is almost a constant finding. Hemolysis is of common occurrence; it is a factor in the production of the anemia and is the source of hemosiderin that is widely deposited (hemochromatosis). The blood platelets may be strikingly diminished and in the terminal phases of the disease, purpuric manifestations are not unusual. However, it is speculative to assume a direct relationship between the thrombocytopenia and these hemorrhagic tendencies (Eagle [4]).

The origin of the Gaucher cell is not definitely known. Mandelbaum and Downey [13] and Kettle [10] stated their conviction that it probably arises from the reticulum cell. Erf [6] studied fresh Gaucher cells as seen in supravital preparations and found that morphologically they are similar to reticulum cells. Pick [15] took exception to the inclusion of Gaucher's disease as a reticuloendothelial disease or a histiocytomatosis, because, " in addition to the reticulum cells of the liver and spleen, the parent cell includes also the connective tissue cells of the blood vessels of the adventitia and periadventitia and, in addition, the cells of Glisson's capsule."

Pathology. The primary pathologic feature is the Gaucher cell. " They have a distinctive appearance [13]; they are fibrillated and show a characteristic longitudinal streaking. They are often elongated and fused into long strands. The nucleus, multiple as a rule, is often irregular in outline, eccentric in position and wrinkled in appearance." As many as 21 have been encountered in one cell.[15] The cells measure from 20 to 80 μ in their largest diameter. The large cell infiltration is usually limited to the spleen, liver, lymph nodes and bone marrow; an instance of renal invasion was reported by Horsley et al.[9] In the spleen, the venous sinuses are lined by Gaucher cells, obliterating the Malpighian corpuscles and crowding the normal pulp cells into enveloping bands. Similarly, the parenchyma of the liver may be " crowded out," the liver lobules disintegrated and a peculiar cirrhotic thickening of Glisson's capsule may occur.[15] Hemosiderin is deposited widely; it is found in the cells of the splenic trabeculae, in the endothelial cells of the venous sinuses (histiocytes) and in the Gaucher cells as well.

Treatment. Potter and McRae [16] report apparent improvement and decrease in the size of the spleen following the continued oral administration of liver extract. Pick [15] would limit splenectomy only to those cases in which anemia is prominent, a hemorrhagic diathesis is manifest or a tremendous spleen is producing mechanical obstructive symptoms. He noted involvement of the osseous system, beginning and progressing rapidly after splenectomy. This also occurred in the case reported by Melamed and Chester.[14] There has been no enthusiasm for the results following irradiation of the spleen.

Case Discussion. The problem presented for diagnosis was one of

hemolytic anemia complicating a tremendous splenomegaly. The patient presented a typical tower skull; hemolytic activity was evidenced by an increasing anemia, a leukocytosis, increased erythrogenic activity of the bone marrow and an increased icterus index; an occasional microcyte that appeared spherical on wet preparations, was seen; all favored a diagnosis of congenital hemolytic jaundice. On the other hand, the tremendous size of the spleen, the general pigmentation of the skin, the symmetrical pigmentation of his legs and the prominent pingueculae seemed conclusive of Gaucher's disease. A marked thrombocytopenia was considered as an added characteristic. The roentgen-ray studies of the bones were not conclusive. Repeated myelograms failed to reveal a single Gaucher cell after careful search. It was remarkable that with a depression of the platelets to 20,000 per cubic millimeter there were no purpuric manifestations. Liver extract, for a number of years, had apparently been able to maintain a fair hemic state. However, in the several months preceding his second admission to the hospital, it proved unable to interrupt the progress of an increasing hemolytic anemia. It was agreed that splenectomy was indicated. Following the removal of the spleen the hemoglobin and red blood cell values progressively improved, to reach normal in five months and have continued so since. Excepting for the areas on his legs, pigmentation is no longer evident; his skin is fair and the pingueculae have disappeared. Subsequent roentgen-ray studies of the bones (19 months after splenectomy) show no evidence of bone lesions. The liver has not enlarged. An ulcer of his leg, of years' duration, promptly healed, and has not recurred. Unusually low blood cholesterol values were obtained before operation.

Summary

A case of Gaucher's disease in a man of 41 has been presented. Liver extract which had apparently been helpful in maintaining a fair hemic level, ultimately became ineffective. An active hemolytic anemia was the indication for splenectomy, by means of which a remission was induced. The spleen weighed 6822 grams. The patient has shown remarkable continued improvement since the operation, including the disappearance of the pingueculae and the general pigmentation.

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Part II. Lipid Analysis

Recently our attention was called by Dr. Harry Mandelbaum to the fact that a spleen would be removed from a patient suspected to be suffering from Gaucher's disease. This gave us an opportunity to survey the literature and select a method for the lipid analysis of the spleen before its actual removal from the patient. Analyses on freshly removed Gaucher's spleens are rare; most have been performed on formaldehyde-fixed specimens. It has been shown that specimens so preserved undergo changes in their lipid composition.[6, 7]

The method selected for the analysis was based upon that of Sobotka, Glick, Reiner and Tuchman.[13] Our procedure differed in that we extracted all the lipids first and fractionated them subsequently, whereas Sobotka and his associates fractionated by extracting with preferential solvents.

The general scheme of analysis involved a preliminary extraction of the fresh spleen with hot alcohol followed by ether. The combined extracts were purified by re-solution in hot absolute alcohol and absolute ether in order to eliminate inorganic material. Cerebrosides and phospholipids were

separated from sterols and neutral fat by the addition of acetone to the residue left after evaporating the absolute alcohol and ether, the cerebrosides and phospholipids being insoluble in this solvent. These two fractions were then analyzed for nitrogen, phosphorus and free and total cholesterol.

In the calculations, the phosphorus values were assumed to be derived from lecithin. Esterified cholesterol was assumed to be cholesterol oleate. The difference between the weights of the acetone-soluble residue and the combined weights of phospholipids, cholesterol and cholesterol esters was assumed to be neutral fat and free fatty acids. The difference between the weights of the acetone-insoluble fraction and the phospholipids was expressed as the cerebroside fraction. The method of isolating the kerasin from the spleen and its properties was described in a separate paper.[8] Pure kerasin was isolated from a large weight of spleen and its identity proved by the selenite plate test [12] and the formation of the methyl ester of lignoceric acid on acid hydrolysis in methyl alcohol.

Procedure

Fifty grams of finely hashed spleen, which had been preserved in a well-stoppered bottle by the addition of a few drops of chloroform, were suspended in 100 ml. of boiling 95 per cent alcohol. The suspension was refluxed one hour and then filtered while hot into a weighed beaker. The alcoholic filtrate was evaporated to dryness at 60° C. according to Kirk et al.[10] This procedure was repeated nine times more, making 10 extractions in all. The residue was then further extracted an equal number of times with 100 ml. portions of ethyl ether. The ethereal filtrates were collected in the same weighed beaker which was reweighed after evaporating the ether to dryness. The lipid-free splenic residue was dried at 100° C. for a few hours and weighed. This weight and the weight of the material in the weighed beaker represent the dry weight of the spleen.

To purify the lipids extracted, the residue in the beaker was reëxtracted with boiling absolute alcohol and filtered. The filtrate was collected in a weighed beaker. The residue was washed several times with boiling absolute alcohol and finally with absolute ether. The combined filtrates were then evaporated to dryness at 60° C. The weight of this extracted material was taken to represent the lipid content of the sample.

The lipids were fractionated by extraction with boiling acetone. The material insoluble in boiling acetone was washed several times with successive portions of boiling acetone and then dried in a vacuum desiccator and weighed. The acetone filtrate was allowed to cool down to room temperature and the slight precipitate which formed was separated by filtration and added to the acetone-insoluble fraction. It was then washed thoroughly with cold acetone, dried at 60° C. and weighed. The acetone washings, collected in a weighed beaker, were evaporated to dryness and the beaker reweighed.

Weighed amounts of each fraction were dissolved in benzene and made up to a definite volume. Aliquots were then taken for the following analyses:

1. Phosphorus, determined by the method of Fiske and Subbarow.[4]
2. Free and total cholesterol, determined by the method of Kaye.[9]
3. Nitrogen, determined by the method of Stover and Sandin.[15]

The results are presented in tables 1, 2, and 3.

TABLE I

Major Fractions of Gaucher's Spleen

Per Cent Solids	Per Cent Lipid in Solids	% Distribution of Lipids		
		Soluble in Cold Acetone	Insoluble in Cold Acetone	Soluble in Hot, Insoluble in Cold Acetone
25.1	17.6	29.1	68.9	2.0

TABLE II

Per Cent Composition of Lipid Fractions

Fraction	Free Cholesterol	Esterified Cholesterol	Phosphatides	Balance (Neutral fat + acids)	Balance (Cerebrosides)
Soluble in acetone	25.6	6.7	12.2	55.5	
Insoluble in acetone	0	0	46.7		53.3

TABLE III

Lipid Fractions in Fresh Gaucher's Spleens. Per Cent Composition of Total Lipids

	Free Cholesterol	Esterified Cholesterol	Phosphatides	Neutral Fat and Fatty Acids	Cerebrosides
Present authors	7.6	2.0	36.2	16.5	37.6
Sobotka et al.[13]	11.6	0.5	17.7	33.6	36.6
Three Gaucher spleens	6.5	7.5	33.5	26.4	26.1
	4.0	10.2	21.9	35.6	27.9
Average of 3 control spleens, Sobotka et al.[13]	10.7	1.5	41.5	26.9	21.0

The percentage lipid on the dry basis as seen in table 1 is less than that observed by most workers in adults suffering from Gaucher's disease.[13, 1, 3, 11] This difference, however, may be due in part to the fact that the spleen lipids were purified in our case from most inorganic substances by reëxtraction of the lipid extract with anhydrous alcohol and ether. The nitrogen content of the acetone soluble fraction was 2.43 per cent. This amount is higher than would be required for the phosphatides; thus the pres-

ence of other nitrogen containing substances is indicated. This may possibly be due to some urea, as shown recently by Christensen [2] and Folch and Van Slyke [5] for the lipid extracts of blood. In the acetone insoluble fraction, the nitrogen content was 4.63 per cent which is higher than the amount required for the phosphatides and cerebrosides. Here again it is possible that some urea was present. Thus both the cerebroside and the neutral fat and fatty acid fractions are over stated by the amount of nitrogenous contaminants present.

The acetone extraction as seen in table 2 effected a cleancut separation of cholesterol and its esters but not of the phosphatides. The solubility of neutral fat and fatty acids in acetone is similar to that of cholesterol and its esters, and therefore a complete separation of these constituents by means of this solvent was probably accomplished.

In table 3, the results obtained are compared with the analyses of Sobotka et al.[13] The neutral fat and fatty acids are lower in our spleen than those obtained by Sobotka et al.[13] even in their normals, while phosphatides and cerebrosides are higher than those of their Gaucher's spleens. The cerebrosides in our spleen are higher than those obtained in their normals but the phosphatides are slightly lower. The combined cerebrosides and phosphatides are much higher than in their Gaucher's spleens and higher than in their normal spleens. Our findings illustrate even better than do Sobotka's his theory that disturbances in fat metabolism are usually at the expense of the neutral fat portion.[14]

Summary

A Gaucher's spleen was analyzed for lipids. The characteristic lipid constituent, kerasin, was isolated and identified. An increase of the cerebrosides at the expense of neutral fat was observed.

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ELECTROENCEPHALOGRAPHIC CHANGES DURING HYPERVENTILATION IN EPILEPTIC AND NON-EPILEPTIC DISORDERS *

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THE clinical observation that attacks of petit mal can be induced by hyperventilation led us to the utilization of this procedure as a routine measure in electroencephalographic examination of patients with known or suspected epilepsy. Since the casual electroencephalographic examination of such patients in the interval between attacks frequently resulted in normal records, it was felt that a higher percentage of positive records could be obtained if the patients were hyperventilated during the examination. This expectation was borne out not only in petit mal epilepsy but also in grand mal, but, because of previously reported changes in the electroencephalogram produced by hyperventilation in normals, it was necessary to compare the changes in epileptics with those obtained in non-epileptics to determine the reliability of the findings as a diagnostic criterion of the presence of an epileptic type of cerebral dysrhythmia. The effect of hyperventilation on the electroencephalogram of 50 patients with known epileptic disorders was, therefore, compared with the effect of this procedure on 50 non-epileptic patients.

METHOD

The epileptic group was composed of patients with idiopathic grand mal epilepsy, petit mal epilepsy, mixed grand and petit mal disorders, and patients with symptomatic epilepsy secondary to organic disease of the brain. The non-epileptic group was a mixed one being composed of some normals and patients suffering from functional and organic diseases of the nervous system.

At the beginning of the investigation, records were taken with a two channel ink-writing electroencephalograph but this was later replaced by a four channel ink-writing electroencephalograph built by Mr. A. M. Grass of the Harvard Medical School. Recordings of the same patient, with the two machines were practically identical.

Simultaneous recordings from the right and left hemispheres with the electrodes placed in the frontal, motor and occipital regions on each side were generally taken on all patients. In some patients, temporal, parietal

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and vertex leads were also applied when more accurate localization of a pathological focus was desirable. Many of the patients were examined on two or more different occasions.

Before records were taken, the patients received instruction concerning the hyperventilation. They were asked to inhale and exhale as deeply and as rapidly as possible. They were told to disregard a feeling of light headedness, if it came on, and in most of the patients, the coöperation was excellent.

A record of at least several minutes' duration, and in many of the patients for a much longer time, was taken with the patient in a resting state. At a verbal command, hyperventilation was begun, and it was continued for two to five minutes. In some cases, it was necessary to encourage the patient to continue the hyperventilation for the desired length of time. The record was continued during the period of hyperventilation and always for several minutes after hyperventilation had stopped.

All records showing high amplitude, slow waves varying in frequency from 2 to 4 per second, with or without spikes or notches, occurring in brief bursts or long runs, were considered definitely abnormal, since we found, as have others, that this dysrhythmia occurred not only in petit mal but also, though not as consistently, in grand mal epilepsy in the interval between attacks.

Records showing numerous slow waves of low amplitude (less than 100 microvolts) or isolated brief runs (less than one second) of slow waves whose amplitude was only slightly greater than the alpha activity were considered questionably abnormal.

When artefacts caused by movement or muscle tremor were excluded, pure spike activity was seen to be a very infrequent finding. All records were analyzed for the occurrence of bursts or runs of the high amplitude, slow waves, and comparisons made between the records before and during (or after) hyperventilation.

In this study, we were not concerned with asymmetries between the two sides, or with irregularities in frequency of the alpha activity which were seen in many of the patients with organic brain disease, though these findings were important in the interpretation of individual records.

Records taken before hyperventilation, with the patient quiet, will be referred to as spontaneous records.

Results

Idiopathic Epilepsy. Of 22 patients with grand mal epilepsy, only four had definitely abnormal spontaneous records, and 15 had records which were questionably abnormal. During hyperventilation, 18 of the 22 patients, or 82 per cent, had abnormal records with typical outbursts or long runs of high amplitude, slow waves, in many cases with spikes or notching, and four patients had questionably abnormal records (figure 1). In the petit

mal group, two of three patients had abnormal spontaneous records and one a questionably abnormal record. During hyperventilation, all three patients had definitely abnormal records. In the group with both grand and petit mal epilepsy, two of six patients had definitely abnormal spontaneous records. During hyperventilation, five had definitely abnormal records (figure 2). Of 31 patients, therefore, with idiopathic epilepsy, only eight showed abnormal spontaneous records, while 26 or 84 per cent showed abnormal records during hyperventilation.

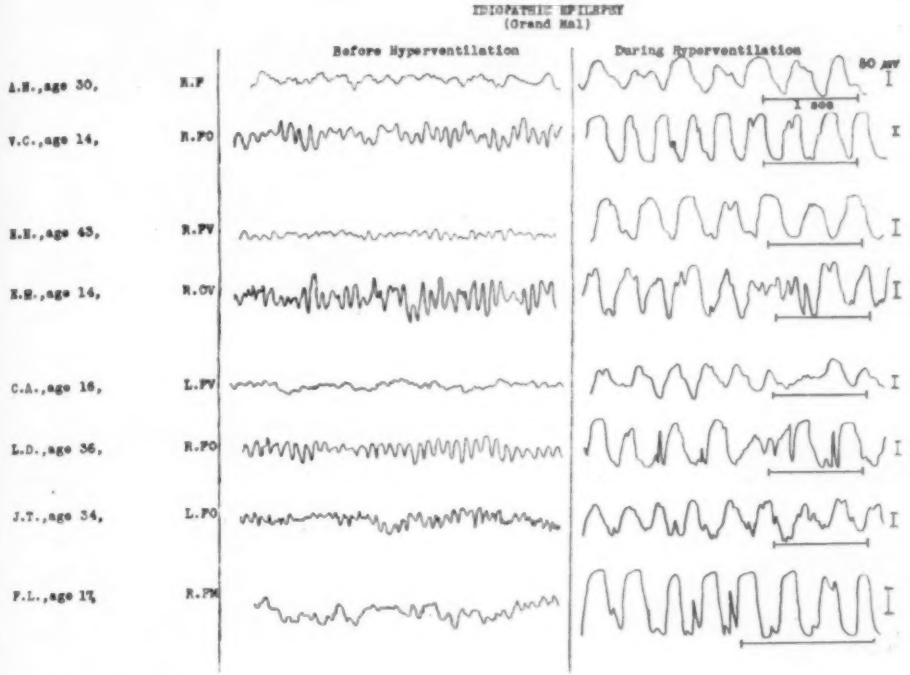

FIG. 1. Sections from electroencephalograms of eight patients with idiopathic grand mal epilepsy. A marked dysrhythmia is induced in each case by hyperventilation. In some cases, as in L. D., the spontaneous record is normal. The initials at the left of the spontaneous records refer to the areas of the skull from which the recordings were taken: F., M., O., V., representing Frontal, Motor, Occipital and Vertex. R. and L. refer to right and left. The amplification and time scale varies in the different records. The marker at the extreme right indicates the size of a 50 microvolt signal, and the horizontal line under the record indicates an interval of one second. The same symbols will be used in subsequent figures.

Symptomatic Epilepsy. In the group with symptomatic epilepsy, four of 19 patients showed the typical spontaneous outbursts of the high amplitude, slow waves, while during hyperventilation, 10, or 53 per cent, were definitely abnormal (figure 3). In this group, six patients had normal records before and during hyperventilation.

Non-Epileptic Group. The non-epileptic group consisted of patients with organic disease of the brain, patients with psychoneuroses and normals.

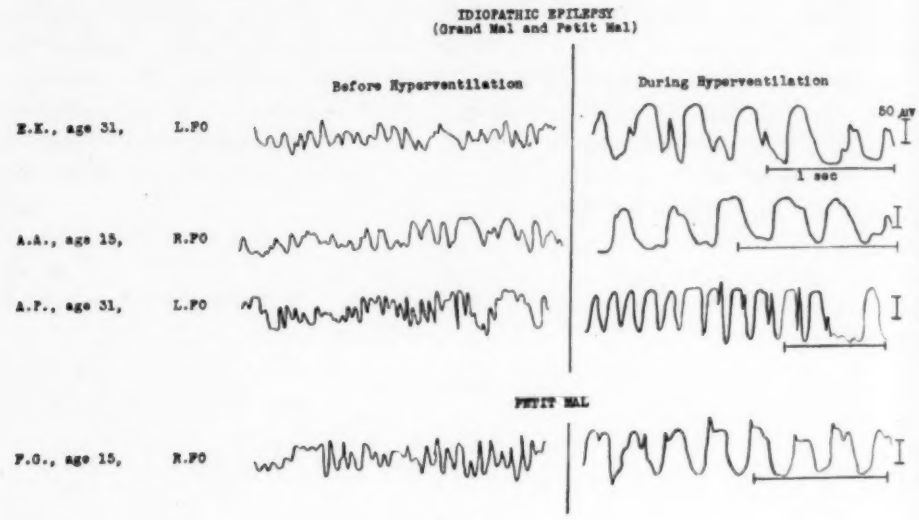
IDIOPATHIC EPILEPSY
(Grand Mal and Petit Mal)
Before Hyperventilation
During Hyperventilation
E.K., age 31, L.FO
50 μV
1 sec
A.A., age 15, R.FO
A.P., age 31, L.FO
PETIT MAL
F.G., age 15, R.FO

FIG. 2.

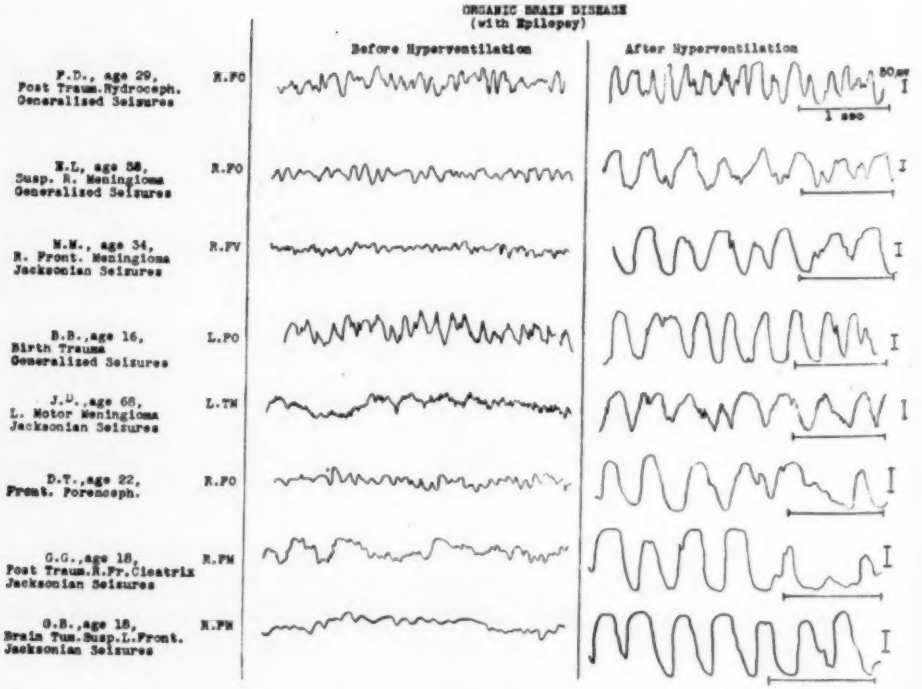
ORGANIC BRAIN DISEASE
(with Epilepsy)
Before Hyperventilation
After Hyperventilation
F.D., age 29, Post Traum.Hydroceph. Generalised Seizures R.FO
50μV
1 sec
M.L, age 58, Susp. R. Meningioma Generalised Seizures R.FO
M.M., age 34, R. Front. Meningioma Jacksonian Seizures R.FV
B.B.,age 16, Birth Trauma Generalised Seizures L.FO
J.D.,age 68, L. Motor Meningioma Jacksonian Seizures L.TM
D.T.,age 22, Front. Porenceph. R.FO
G.G.,age 18, Post Traum.R.Pr.Cicatrix Jacksonian Seizures R.PM
G.B.,age 18, Brain Tum.Susp.L.Front. Jacksonian Seizures R.PM

FIG. 3.

The group with organic disease of the brain included patients with cerebral arteriosclerosis, brain tumors, Sydenham's chorea, degenerative disease of the nervous system, multiple sclerosis, dystonia musculorum deformans, general paresis, encephalitis, Alzheimer's disease and post-traumatic encephalopathy.

Of 25 patients comprising this group, five showed abnormal spontaneous records. Four of these were patients with chorea and one was a patient with a temporal lobe glioma who had experienced episodes of loss of consciousness without any convulsive phenomena. During hyperventilation, 12, or 48 per cent, showed abnormal records (figure 4). It is of great in-

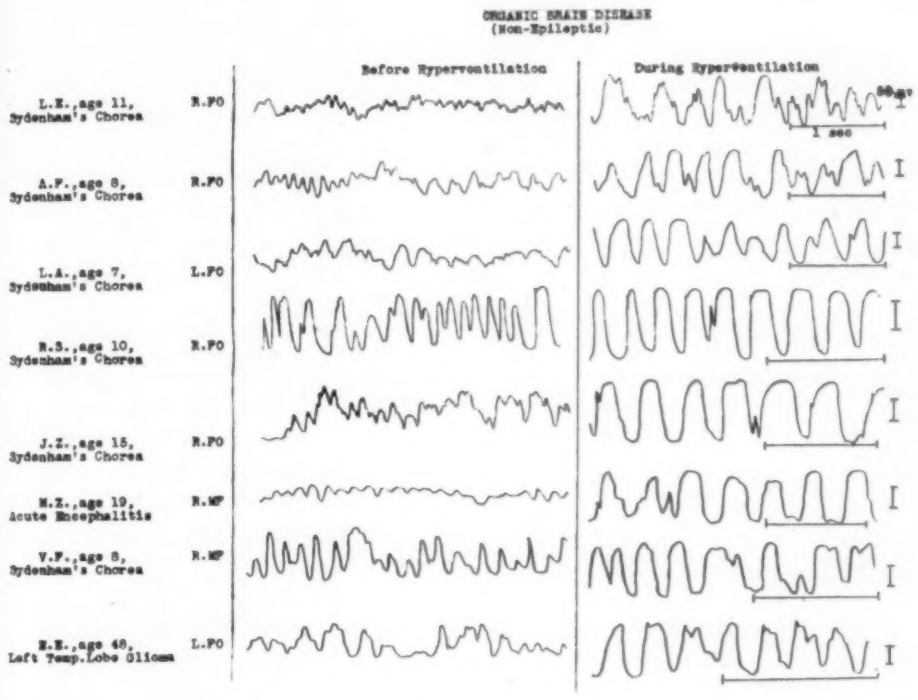

FIG. 4.

terest to note that of eight patients with Sydenham's chorea, all showed abnormal records during hyperventilation.

There were eight patients in the psychoneurotic group. All of them had normal records before and during hyperventilation.

Records were obtained on nine normals. None had abnormal spontaneous records. Hyperventilation produced no significant change in any of the records.

The miscellaneous group consisted of four patients with migraine, two with severe behavior disorders, one with dizziness of undetermined cause and one with hyperparathyroidism. Of these, none showed an abnormal

spontaneous record, whereas during hyperventilation, four showed definitely abnormal activity of the epileptic type (figure 5). Two of these four had migraine and two were the children with severe behavior disorders.

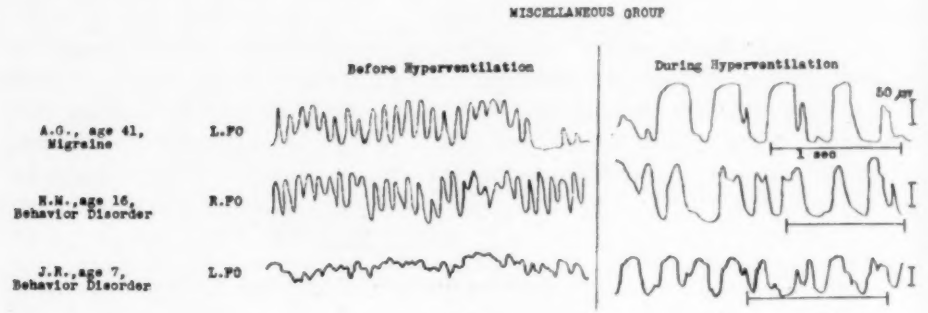

FIG. 5.

Throughout the entire series, in practically all the records which were abnormal while the patient was at rest, the abnormality became much more pronounced during hyperventilation (table 1).

TABLE I

Comparison of Electroencephalographic Findings with Regard to Epileptic or Epileptic-like Activity Before and During Hyperventilation

	Before Hyperventil.			During Hyperventil.		
	Abn.	Quest. Abn.	Norm.	Abn.	Quest. Abn.	Norm.
Epileptic						
Grand Mal	4	15	3	18	4	0
Petit Mal	2	1	0	3	0	0
Grand and Petit Mal	2	3	1	5	1	0
Symptomatic	4	6	9	10	3	6
Non-Epileptic						
Organic brain dis.	5	7	13	12	9	4
Psychoneuroses	0	0	8	0	0	8
Miscellaneous	0	1	7	4	2	2
Normals	0	0	9	0	0	9

DISCUSSION

It has been known for some time that hyperventilation causes changes in the electroencephalogram. Gibbs, Davis and Lennox [1] drew attention to the fact that overbreathing produced in normals a gradual decrease in the predominant activity to waves of one to five per second of increased amplitude. These changes were similar to those seen in cerebral anemia (fainting) and when anoxemia is produced by breathing nitrogen.

Lennox, Gibbs and Gibbs [2] reported that voluntary hyperpnea in epileptics and normals resulted in potentials which are slow and of large volt-

age; and in patients with petit mal, in large slow waves which were followed by typical petit mal waves. Jasper, Solomon and Bradley [3] in their electroencephalographic studies of behavior problem children obtained continuous spike and slow activity with hyperventilation in many children who spontaneously showed irregular petit mal activity.

Cobb, Sargant and Schwab [4] found that the amount of petit mal activity varied directly with the volume of air respired per unit of time. In a recent contribution, Osgood and Robinson [5] reported the electroencephalographic findings of 38 patients who had been free of attacks for five or more years. Three of the patients showed wave and spike formations and these only during hyperventilation. They mentioned the importance of hyperventilation in establishing the abnormality of an electroencephalographic record. Ten of their patients had normal records until they overbreathed.

Jung,[7] working in Germany, also stressed the importance of hyperventilation in releasing specific epileptic dysrhythmias. Using this procedure, he obtained abnormal records in four-fifths of all patients with idiopathic epilepsy who were examined.

In a later communication, Gibbs, Lennox and Gibbs [6] pointed out that blood CO_2 values tend to be abnormally low in patients with petit mal, this finding being consistent with the fact that hyperventilation tended to precipitate overt petit mal attacks. In contrast to this, they reported a tendency to high CO_2 values in patients with grand mal seizures. They claimed that these observations were consistent with the contrasting types of cerebral dysrhythmias seen in grand and petit mal epilepsy, the former being rapid and the latter slow. In our series, we did not observe these contrasting dysrhythmias in the interval between attacks. In the grand mal group, fast activity was not the characteristic type of abnormality. Our patients, however, were not examined just prior to attacks. In only two patients with grand mal epilepsy, one patient with symptomatic epilepsy, and one patient with petit mal epilepsy was rapid spike activity outstanding.

The outstanding abnormality that we observed in grand mal, occasionally in spontaneous records, and generally during hyperventilation (v.s.) was bursts of slow waves of increased amplitude, frequently with notches or spikes similar to, and at times not distinguishable from, the characteristic wave and spike activity of petit mal. This same type of activity, however, was seen in patients with symptomatic epilepsy and patients with organic disease of the brain without epilepsy but not in the normals or in patients suffering from psychoneuroses. When such activity was present in a resting state, it generally became more pronounced during hyperventilation. In a majority of the epileptics and in many of the non-epileptics with organic brain disease, it was induced by hyperventilation. It also appeared during hyperventilation in two patients with migraine and in the two children with behavior disorders included in this series. Many other children with behavior disorders, whom we examined but did not include in this study, showed similar findings.

It is to be emphasized that from none of the patients, except those with petit mal, who showed this petit mal-like activity could a history of petit mal be elicited, nor was there any apparent or admitted disturbance in consciousness during the examination. Unfortunately, the reaction time of the patients was not tested as was done by Schwab [10] during bursts of the abnormal activity. However, even if the reaction times were found to be increased, it could not be assumed that a specific petit mal disorder existed.

That the abnormal activity was not caused by tetany was proved many times in the course of this study. During hyperventilation in many patients, there were overt signs of tetany without any disturbance in the electroencephalogram. In no case—showing abnormal activity, did tetany appear simultaneously with the abnormality in the record. In some instances, the tetany appeared before and in some after. Many times, the tetany was present long after the record had returned to normal. Nor were the abnormalities a result of disturbances in consciousness or faintness produced by hyperventilation. In no case did these complications supervene. This is similar to the experience of Jung,[7] who emphasized the fact that the specific epileptic dysrhythmia produced by hyperventilation did not occur in tetany, cardiac attacks or spells of dizziness. Also, it is to be emphasized that there is a marked difference between the slow waves described by Gibbs and his co-workers, as occurring in normals in states of impaired consciousness, and the dysrhythmia produced in our cases during hyperventilation.

Many of the patients were examined several times and most of them showed the same type of disturbance in the repeated examinations; in two cases, however, the findings were not constant. The effect of sedation on the above findings was not studied.

Quantitative studies on the amount of hyperventilation were not possible in the entire series. Even though all the patients coöperated well, by breathing deeply and rapidly, variations in the total volume of air respired, of course, existed. It was our impression, however, that if abnormal activity appeared, it did so before 180 seconds of hyperventilation, or not at all. In an attempt to confirm this, we measured with a Benedict Roth Metabolism Apparatus (made by Warren E. Collins, Inc.) the total amount of respired air during hyperventilation in three known epileptics and in three normals (table 2). One of the epileptics, breathing at a rate of 18.7 liters per minute, developed outbursts of the high amplitude, slow waves after two minutes or after having breathed 37.4 liters of air. Another epileptic, breathing 33.1 liters per minute, developed the epileptic activity after 80 seconds or after having breathed approximately 44 liters of air. The third epileptic, breathing 54.4 liters per minute, developed the first outburst of abnormal activity after one minute.

When the normals were examined, the findings were quite different. One hyperventilated 136.5 liters in five minutes, or 27.3 per minute, another 291 liters in five minutes, or 58 liters per minute, and a third 132.1 liters in

TABLE II

Effect of Hyperventilation in Producing Epileptic Dysrhythmia

Dysrhythmias were induced in the epileptics with relatively little hyperventilation, while no significant change resulted from much longer hyperventilation in normals.

	Duration of Hypervent.	Liters per Minute	Total Respired Air	Result
Epileptic				
1	120 sec.	18.7	37.4	+
2	80 "	33.1	44.0	+
3	60 "	54.4	54.4	+
Normals				
1	300 sec.	27.3	136.5	0
2	300 "	58.0	291.0	0
3	262 "	30.2	132.0	0

4⅜ minutes, or 30.2 liters per minute, and none showed any significant change in the records.

While not conclusive, the above findings indicate that it is not merely the overbreathing which is responsible for the appearance of the abnormal activity we have found. It would appear that there must be an additional factor of predisposition to dysrhythmia.

It is not surprising to find in grand mal epilepsy, a dysrhythmia similar to that seen in petit mal, for certainly from the clinical standpoint, they are closely related. The facts that the two conditions so frequently occur together and that one frequently replaces the other, and that their response to medication is so similar, have led to the clinical recognition of their being different manifestations of a single disorder. That such dysrhythmias occur, however, in other conditions casts serious doubt upon the specificity of the findings in epilepsy.

That there might be some relationship between epilepsy and the other conditions showing similar disturbances in the electroencephalogram was considered, but a careful analysis of our findings produced no evidence which would support such a hypothesis. It would seem then, that what has in the past been considered a specific epileptic dysrhythmia, is, in reality, one of the common modes of electroencephalographic expression of a physiological disturbance in the brain. The variety of conditions in which this disturbance becomes manifest seems to indicate the absence of any one pathological basis for the disturbance. Jung,[7] apparently of the same opinion, stated that a reliable differentiation between idiopathic and symptomatic epilepsy was not possible.

By what method hyperventilation releases the dysrhythmia, and what the significance of the dysrhythmia is, we do not know. We are confronted, however, with the fact that hyperventilation causes the appearance of the dysrhythmia in some and not in others.

Two additional factors must be considered: (1) the degree of change in the blood CO_2 produced in an individual by a specific amount of over-

breathing; and (2) the sensitivity of the brain cells to the change in blood CO_2. It would seem that those patients who have either a disturbance in the regulatory mechanism of blood CO_2 with normally functioning brain cells, or damaged brain cells which are abnormally responsive to changes in blood CO_2 in the presence of a normal regulatory mechanism, are apt to develop the same dysrhythmia during hyperventilation.

After having found abnormal concentrations of blood CO_2 in epileptics, and after having observed that the chemical changes in the blood induced by hyperventilation differed in patients with petit mal from those in normals, Gibbs, Lennox and Gibbs suggested that idiopathic epilepsy might be the result of a disturbed regulation in blood CO_2. A similar disturbed physiology may also exist in the relatives of the patients with epilepsy and chorea and in the patients with migraine who showed identical dysrhythmias during hyperventilation. While this same mechanism may be at work in the patients with organic brain disease who showed the same abnormality in their electroencephalograms during hyperventilation, there is a great likelihood that the damaged cortical cells are unusually sensitive to normal changes in the blood CO_2. This certainly appears to be the case in those patients where the outbursts of high amplitude, slow waves were confined to, or predominated in, the area around the lesion.

We have subjected a group of children without any known disease of the brain to hyperventilation and have obtained records in a large number of them which are not distinguishable from those seen in epileptics. We do not know whether this is the result of abnormal fluctuations in blood CO_2 during hyperventilation or increased sensitivity of the cortical neurons in connection with the patients' ages.

Concerning the significance of the dysrhythmia, we feel that it may be a regression to a more primitive type of cortical activity. There are many facts in support of this. The electroencephalogram of infants is characterized by slow activity. As cortical activity differentiates and matures, the gross synchronization of large groups of cells becomes more and more interrupted, giving rise to an increasing number of independently functioning smaller neuronal pathways and discharges, transforming a rhythm of three to four per second to a ten per second activity that characterizes the adult record. When the normal physiology of the brain is disturbed by spontaneous or induced abnormal fluctuations in the blood chemistry, or when a diseased brain becomes unusually hyper-sensitive to normal variations in blood chemistry, a more primitive activity appears. It is analogous to the clinical observation that the newly acquired functions of the cortex are lost first when the cortex becomes diseased. It is interesting to note that Blake, Gerard and Kleitman [8] reported the occurrence of high amplitude, slow waves which are similar to those seen in epilepsy, in the stage of deep sleep. High amplitude, slow activity and, in places, wave and spike formations were also described by Hoagland and his co-workers [9] in the electroencephalograms of dogs anesthetized with nembutal. Adults in states of impaired

consciousness show slow activity, and it may be significant that children without brain disease are much more prone to develop the dysrhythmia than normal adults. We feel that this may be an important factor aside from the encephalitis in the obtaining of such a high percentage of abnormal records in the children with Sydenham's chorea.

The results of this study in themselves, as can be seen, leave many questions unanswered. They do, however, seem to indicate that the dysrhythmia seen in epilepsy is not specific for that condition, and suggest that the tendency to dysrhythmia may be related to age as well as to heredity.

Summary and Conclusions

1. The electroencephalographic changes during hyperventilation were studied in 50 epileptics and compared with the findings in 50 non-epileptics.

2. It was found that the dysrhythmia which is observed in idiopathic epilepsy occurs in other conditions associated or not with a convulsive state, and, therefore, cannot be considered as pathognomonic of the convulsive state. The occurrence of the dysrhythmia in adults, however, cannot be considered normal.

3. Hyperventilation can exaggerate an already existing dysrhythmia or release a latent dysrhythmia.

4. There is some indication that the tendency to dysrhythmia is related to age as well as heredity.

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CERTAIN INFECTIONS IN THE BACKGROUND OF PATIENTS WITH CORONARY OCCLUSION *

By JOHN T. KING, M.D., F.A.C.P., *Baltimore, Maryland*

FOR some years the question of etiology has held a fascination for many of us who are interested in the cardiovascular disorders of middle and late life. In what way do persons who experience a sudden occlusion of a coronary artery at the average age of about 60 years differ from the generality of mankind? Are they members of unfortunate families, victims of improper habits of activity or diet, or do they smoke, drink, or exercise too violently? Is the "pace of modern life" too brisk or demanding?

I confess to an inability to establish a constitutional type as a common denominator. The "high pressure" business executive or busy doctor is followed by the college professor or the clergyman. While the businessman or doctor may work too hard and smoke too much, the professor and clergyman have led lives free of unhygienic stigma. In analyzing 150 cases of coronary occlusion from his practice, Blumer [1] found that 52 per cent were total abstainers from alcohol, 34 per cent drank occasionally, 14 per cent habitually; 34 per cent smoked nothing, 36.6 per cent were moderate smokers, 30 per cent excessive.

Diabetes is a well known cause of coronary sclerosis, as it is of general arteriosclerosis, and may be incriminated as a cause of certain cases of coronary occlusion. Polycythemia is another cause of angina pectoris or coronary occlusion. However, these conditions can be held responsible for only a small proportion of the total cases.

Sex is a factor. Only one of each five cases in my practice is in a woman. It is interesting to note that some of the women affected are of the *typus masculinus*, at least as regards habits of work and play. Although such cases do occur, coronary occlusion is very rare before the age of 60 among women leading the protected life of a housewife.

Searching for a common denominator among such factors as constitution, working habits, smoking and drinking habits, heredity and exercise, has proved nothing to my satisfaction. Sex is a denominator of 80 per cent. But even supposing that all cases occurred in men, we would still lack an explanation for the occurrence of premature coronary disease in certain individuals.

For some years I have been impressed by the frequency with which I encounter the history of excessive upper respiratory infection or rheumatic fever in the background of my private patients with coronary artery disease. Fortunately, although my practice tends somewhat toward cardiovascular

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disorders, it is by no means limited. It has been driven home to me, through the constant reports of intelligent persons, that such infections are rather excessive among cases of coronary occlusion, both as regards intensity and repetition. Now, having accumulated a considerable number of cases, I am undertaking to analyze them and to compare them with proper control cases.

The literature contains many intimations regarding the infection theory, though it is not very conclusive. Gross and Oppenheimer [5] are skeptical, reporting that "despite the rather frequent involvement of the coronary arteries during the course of acute rheumatic fever, it has not been possible to establish such an entity on clinical grounds." Perry [12] found that the coronary arteries are usually affected in rheumatic carditis; the lesion is a panarteritis, consisting of: (*a*) intimal thickening more or less cellular; (*b*) degenerative and inflammatory lesions of the intima; (*c*) inflammatory infiltration of adventitia. Klotz [10] reports the large coronary arteries to be inconstantly affected, the smaller branches very constantly, by the rheumatic infection. Christian [3] holds the view that, in coronary disease, the artery is most often the seat of arteriosclerosis; while, at other times, an arteritis, possibly resulting from syphilis or bacterial infection, is found. He thinks arteritis plays an important part, especially in younger individuals who have not had syphilis.

More specifically, Jones and Rogers [7] suspect a streptococcus in the etiology of cardiovascular disease, including coronary thrombosis. In 11 cases of death from coronary occlusion, the vessel in only one showed much narrowing due to arteriosclerosis. In the others were found fresh clots; sections showed lymphocytes, plasma cells, diplococci and short chain cocci. These organisms were found in the subintimal proliferative areas and in the outer media and adventitia. In this connection, consider the speculative hypothesis on the pathology of atheroma in the recent volume on the Biology of Arteriosclerosis by Winternitz et al.[14] After a beautiful exposition of the basic pathology of atheromatous plaques, these authors point out certain features of similarity between such lesions and those found in the endocardium as a result of rheumatic infection. It is intimated that such lesions as plaques in the coronary and other arteries may result from bacterial invasion, possibly with the *Streptococcus viridans.*

Typhoid fever has been found to involve the coronary arteries. In 1930, in discussing Klotz's paper, Thayer [13] mentioned the case of a young man dying of typhoid in his third decade of life. At necropsy, an area of endarteritis was found around one coronary artery; had this patient lived, the lesion would have led to coronary constriction and provided a favorable site for occlusion.

Newsholme [11] has pointed out that, while the evil effects of excessive muscular work, overfeeding, alcoholism, and excessive smoking upon the arteries are generally recognized, yet the chief damage to arteries is done by infections. He names rheumatic fever, syphilis, focal and other infections

with pneumococcus or streptococcus. Thus, clinical evidence *in re* the rheumatic infection and the coronary arteries is suggestive, but not conclusive. Evidence bearing on repeated tonsillitis as a possible factor in coronary disease is even more elusive. In 1926, Kahn [9] reported that he had been impressed by the frequent occurrence of acute tonsillitis in the background of his private patients with angina pectoris. Of 82 patients, 24 reported having suffered repeated tonsillitis attacks, 20 gave a history of rheumatic fever, 10 were diabetics; no control cases were reported. As will be shown later, the incidence of tonsillitis in Kahn's patients (29 per cent) is not excessive, as it was reported in 34.5 per cent of my control cases (table 1). However, his figure of 20 cases with rheumatic history (24 per cent) is very high and quite suggestive.

Among my private patients have been found 157 instances of well authenticated coronary occlusion. One case of thrombo-angiitis obliterans, three of diabetes, and two of polycythemia were eliminated; 11 others were unavailable from lack of sufficient data. Thus, 140 cases are available, in none of which was there a background of any of the known or usually suspected etiologic agents.

TABLE I

Comparative Incidence of Infections (in Per Cent)

	Rheumatic Fever	Excessive Tonsillitis	Infected or Scarred Tonsils	No Evidence of Infection
Coronary Occlusion (140)	11.8	52.1	32.1	20
Controls (110)	5.0	34.5	24.5	36.4

Control Cases. For comparison, these were drawn also from my private files, histories of both the coronary cases and the controls having been taken by myself. The proportion of males to females in the coronary group was 79.3 : 20.7 per cent; among the 110 controls the ratio was 79.1 : 20.9 per cent. All patients and controls were white. No case was used as a control in which tonsil infection could be suspected as an important or, perhaps, etiologic factor; thus, all cases of rheumatic valve disease, hypertension, exophthalmic goiter, rheumatoid arthritis and nephritis were excluded. Controls were selected so that each white male and female respectively in the first 110 coronary cases was matched by a male or female of corresponding age in the control group. Comparison of the two groups in per cent is shown in table 1.

Rheumatic Fever. The proportion of 11.8 per cent of patients who gave a history of past rheumatic fever in the coronary group to 5 per cent in the control group is not very striking. However, in the coronary group were four patients with frank rheumatic valve disease, who gave no history of rheumatic fever. Including these, we have 14.6 per cent of coronary cases in which either a history of rheumatic fever or rheumatic valve disease, or

both, was found. Although this is nearly three times as great as the figure for control cases (5 per cent), it is not statistically significant. It would appear that, although the number of patients with coronary occlusion who had had known rheumatic fever is suggestively high, yet the incidence of rheumatic infection is not sufficiently frequent to provide a common denominator.

Excessive Tonsillitis. Of 140 patients with coronary occlusion, 73 (52.1 per cent) had experienced repeated attacks of tonsillitis or quinsy, or both, against 38 (34.5 per cent) among the control cases. Ordinary sore throats, or a single or occasional attack of tonsillitis, were ignored.

Tonsillectomy. Study of the cases in which one or more operations or cauterization had been performed upon the tonsils was not fruitful. Thirty-five per cent of the coronary cases gave a history of such a procedure against 34.5 per cent of the control cases. As these operations were not done on a prophylactic theory, but for relief from chronic or acute infections, they cannot be said to provide evidence against the hypothesis that tonsillitis may affect the coronary vessels. In other words, the harm, if harm there was, could have occurred before the infection was arrested. This is especially indicated since many operations were postponed until adult or middle age.

Age. Dr. C. Holmes Boyd, who has been interested with me in the subject under discussion, pointed out the marked incidence of the suspected infections among the youngest patients with coronary occlusion. Though there were only six such cases in persons under 40 years of age, yet two, and probably a third, had had rheumatic fever. Five gave a history of excessive tonsillitis, and four had had tonsil operations.

Case 1. Male, aged 39. History of rheumatic fever. Tonsillectomy performed, with stump remaining in one fossa.

Case 2. Male, aged 35. History of repeated tonsillitis and cervical adenitis.

Case 3. Male, aged 39. History of rheumatic fever and repeated tonsillitis. Tonsillectomy performed at age of 35.

Case 4. Male, aged 39. No history of tonsillitis or rheumatic fever. Syphilis treated 20 years before.

Case 5. Male, aged 36. Repeated sore throats and two tonsil operations as a child. Put to bed several weeks as child for "enlarged heart and fever"; no arthritis. Thought to have had rheumatic fever.

Case 6. Female, aged 38. Tonsillitis each year until age of 10, when tonsillectomy was done. Chronic antrum infection with fever over period of one year, with two radical operations.

With such reports in mind, one is tempted to jump to the conclusion that, while such infections may be concerned in causing premature vascular damage in younger persons, yet it may be assumed that coronary occlusion in the upper decades of life is merely the result of more or less normal processes of aging. To test this hypothesis, patients were divided according to decades, and their histories compared with those of the control group (table 2). This concept is not supported by the comparison, since it is readily seen that

TABLE II

Incidence of Excessive Tonsillitis among Coronary Cases and Controls, by Decades (in Per Cent)

Age	Controls	Coronary Occlusion
30–40	20	83
41–50	37	40
51–60	43	58
61–70	26	45
Over 70	25	43

the excessive incidence of tonsillitis is not limited to the background of the younger type of patient; it is found at any age. The rather low figure for coronary patients in the fifth decade is difficult to explain.

Clear Histories. It is possible to approach the question from the negative viewpoint, selecting only those cases in which none of the suspected infections was indicated. Thus, certain persons gave no history of excessive tonsillitis, quinsy, or rheumatic fever, showed no evidence of past or present tonsil infection when examined, and had had no operative procedures on the throat. Forty (36.4 per cent) of the control cases fall into this category, against 28 (20 per cent) of those who had had coronary occlusion.

DISCUSSION

To demonstrate a relationship between the suspected infections and coronary occlusion, it must be shown that the infections have been significantly higher in the background of patients with this disorder than among properly selected controls. As stated above, every precaution was taken to match control cases with cases of coronary occlusion, male with male, female with female, age with age. Since we are testing the possible effects of repeated tonsillitis, all cases of diseases in which tonsillitis is suspected of being concerned had to be excluded from the group of controls. Thus, cases of rheumatic valvular disease were excluded. It may be argued that it is not fair to include cases of rheumatic valve disease in the coronary occlusion group, while excluding them from the controls. This point needs discussion.

Among the 140 cases of coronary occlusion, 16 gave a history of past rheumatic fever, while one was thought to have had rheumatic fever. The one probable case was listed as one-half, raising the number to 16.5 (11.8 per cent). In addition to these were found four cases of frank rheumatic valve disease among the coronary cases, in which no history of rheumatic fever was obtained. Thus we have 20.5 cases, or 14.6 per cent, of the coronary group in which the history or valve disease, or both, gave evidence of previous rheumatic infection. Against this figure, 5 per cent of the control group gave a history of previous rheumatic fever. But we have excluded cases of rheumatic valve disease from the control group because of the known relationship between tonsillitis and rheumatic fever. Thus, the

control group may be a superior group rather than an ordinary healthy group. What is the incidence of rheumatic valve disease in the community at large? In other words, how many cases of rheumatic valve disease must be added to the control group to make it comparable with the universe of human beings? In Philadelphia, Cahan [2] has estimated that about 1 per cent of 350,000 school children have some form of heart disease, and that

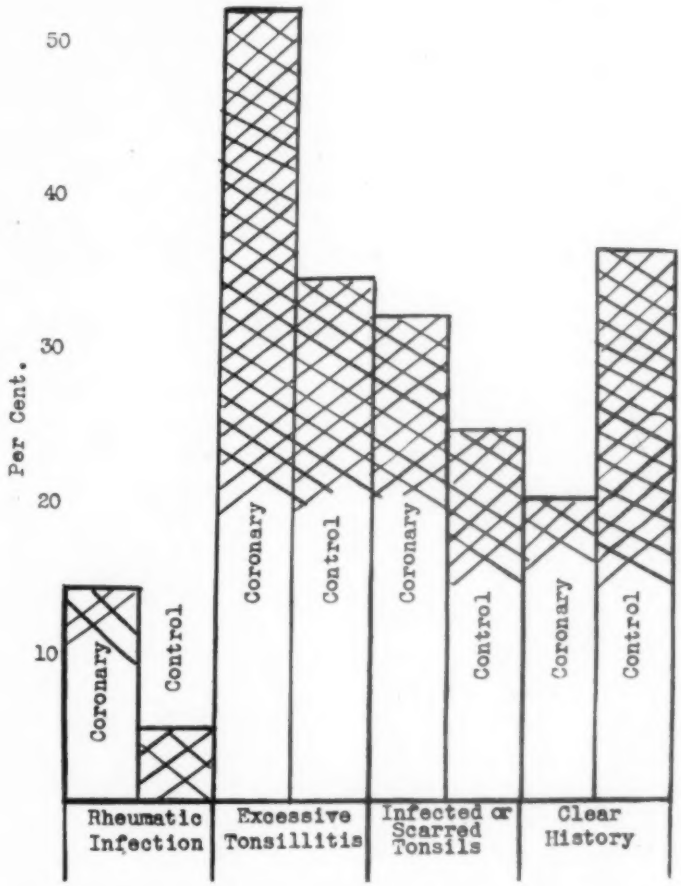

FIG. 1. Incidence of rheumatic and tonsillar infections among cases of coronary occlusion and control cases, in per cent.

rheumatism accounts for most cases. This is the best evidence I have found on the incidence of rheumatic heart disease in a climate similar to that of Baltimore.

The two groups may be compared as follows, with regard to rheumatic infection. Coronary group: positive history in 11.8 per cent plus valvulitis without history in 2.8 per cent = 14.6 per cent. Control group: positive his-

tory in 5 per cent plus (probable incidence of valvulitis in community, but excluded from control group) 1 per cent = 6 per cent.

Now, these numbers are not large, and the results not very convincing. Rheumatic infection as commonly regarded can not be considered a common denominator in the etiology of coronary artery disease. Nevertheless, the incidence of positive histories (11.8 per cent) is suspiciously high for a group derived from private practice, as is also the incidence of rheumatic valvulitis. It is conceivable that coronary disease in a person who has had rheumatic infection is due, not to rheumatic fever, but to the tonsillitis that often afflicts the rheumatic patient.

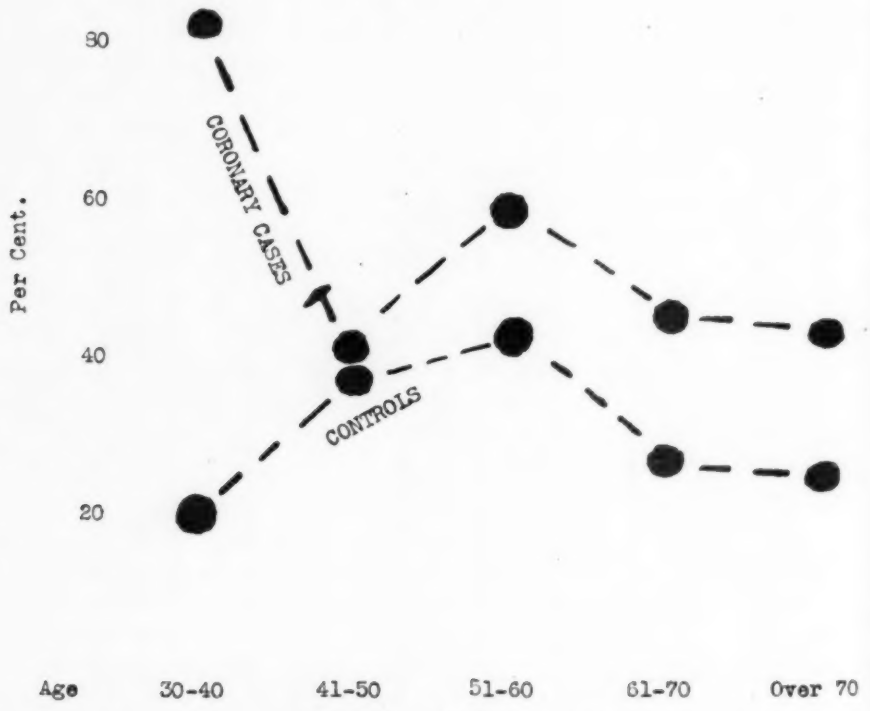

FIG. 2. Graphic representation of incidence of excessive tonsillitis among control cases and patients having coronary occlusion, arranged by decades.

Other Infections. It is hardly necessary to consider tuberculosis or syphilis very seriously as important causes of coronary occlusion. Occasional cases of angina or of coronary occlusion are found due to encroachment of a syphilitic aortitis upon the coronary orifices. However, these cases constitute a small proportion of the total instances of coronary occlusion in private, and even in hospital, practice. Tuberculosis is not a factor.

In analyzing my cases, I found that 12 of 140 patients (8.6 per cent) gave a history of previous typhoid fever. Since the age of all patients with

coronary occlusion is such that they have lived through a period of enormous epidemics of typhoid, such a morbidity figure does not seem excessive. It must also be remembered that Baltimore, where many of these patients have lived for years, held at times the record for the highest incidence of typhoid in the country.

Among the coronary cases, the history of previous pneumonia occurred only a few times, while malaria was even less common.

Many patients in both the coronary group and among the controls had sinus infection or treatment directed at the sinuses. It is very difficult for an internist to estimate the importance of such infections. Although it is reasonable to suppose that serious sinus infections may cause systemic damage in the form of arterial disease, I have found it impossible to arrive at satisfactory evidence.

Tonsillitis. Reliability of histories may be considered high, since all cases in both the coronary and control groups were drawn from my private files. The results are not ideal. Patients suffering from acute tonsillitis may report an ordinary sore throat or no sore throat at all. Others give a completely negative history while presenting obviously infected or heavily scarred tonsils. To balance such errors, the same methods of history-taking and examination were also applied to the control cases.

Is the difference in the incidence of tonsil infection in the two groups sufficient to be significant? In other words, is it likely that the difference between 52.1 per cent of excessive tonsillitis in the coronary group as against 34.5 per cent in the control group (17.6 per cent), is due merely to chance? Here we can apply the formula in common use for determination of the *standard deviation of the difference;* i.e., the scattering of figures that might be considered due to sampling, or the laws of chance. The total figures involved are:

Coronary cases with excessive tonsillitis	73
Coronary cases without excessive tonsillitis	67
Total	140
Control cases with excessive tonsillitis	38
Control cases without excessive tonsillitis	72
Total	110
Total cases in 2 groups	250
Total cases with excessive tonsillitis	111
Total cases without excessive tonsillitis	139

The formula for determining the standard deviation of the difference is:

$$\sqrt{\frac{PQ}{N_1} + \frac{PQ}{N_2}}$$ *

* Dr. Margaret Merrell, of the School of Hygiene and Public Health, Johns Hopkins University, was kind enough to advise me regarding this formula.

in which

$$P = \text{proportion of positive cases} = \frac{111}{250}$$

$$Q = \text{“ “ negative “} = \frac{139}{250}$$

$$N_1 = \text{number in coronary group} = 140$$
$$N_2 = \text{“ “ control “} = 110$$

Thus:

$$\sqrt{\frac{\left(\frac{111}{250}\right)\left(\frac{139}{250}\right)}{140} + \frac{\left(\frac{111}{250}\right)\left(\frac{139}{250}\right)}{110}}$$

The result is 6.3 per cent. Ratio of observed difference to standard deviation of the difference: $17.6/6.3 = 2.8$.

It is common practice in statistical work to consider that a difference in proportion is probably significant if it proved to be two or more times as great as the standard deviation of the difference. We are dealing always, however, with probabilities and not with established fact. Hill [15] states that, when the observed difference is 2.5 or 3 times the standard error, then “differences would occur by chance, roughly, only once in 80 tests and once in 370 tests.” As our figure (2.8) lies between the two, it is quite unlikely that it is due to chance.

In table 1 it is shown that 20 per cent of the coronary cases gave no history of excessive tonsillitis or of tonsillectomy, and presented no evidence of infection on examination. This contrasts with 36.4 per cent of the control group. The observed difference is 16.4 per cent. Is this figure statistically significant? Applying the same formula used above, we find that the standard deviation of the difference in the two groups is 5.7 per cent. The ratio of observed difference to standard error is $16.4/5.7 = 2.9$. This figure, then, is quite high and almost assures (V.S.) that the difference of clear histories in the two groups is not due to chance.

It can not, of course, be said that frequent tonsillitis is necessarily the cause of coronary disease, even if the relationship between tonsillitis and coronary occlusion is a close one from the statistical standpoint. Such a relationship might be explained on the ground that certain persons are of vulnerable constitution and susceptible to both conditions. And what of the many persons who have frequent tonsillitis and who escape cardiovascular damage? The last is hardly pertinent in itself, for innumerable persons suffer repeated tonsillitis and escape rheumatic fever and rheumatic valvulitis; yet the importance of tonsillitis in these states can hardly be questioned.

In recent years a number of investigators (V.S.) have advanced evidence to suggest that some sort of infection may be responsible for coronary artery disease. One of the weak links in the chain of proof has been the lack of *clinical* evidence to show that such infections do occur, and the lack of proof of the nature of such infections. My own impressions were obtained before

the publication of the pathologic and bacteriologic work referred to above. We are still in need of more clinical reports of the type I am attempting here.

Conclusions

1. Excessive tonsillitis occurs in the background of patients with coronary occlusion in a degree of frequency that is beyond reasonable statistical doubt.

2. It is possible that the rheumatic infection should also be suspected as a possible cause of coronary artery damage.

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HETEROPHILE ANTIBODY REACTION CAUSED BY BACTERIAL INFECTION *

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A HUMAN serum was found to contain a high titer of heterophile antibodies even though the patient suffered neither from serum sickness nor from infectious mononucleosis (so-called false Paul-Bunnell reaction). This observation and the results obtained from the study of the antibodies involved, seem to be worth reporting because such reactions are very rare. Also, for the first time, it was possible in this case to explain the serological phenomenon on the basis of an infection with a bacterium containing heterophile antigen.

Sheep hemolysins and agglutinins occurring after immunization with an antigen which is present in the tissues of various animals are called Forssman antibodies.[1] The Forssman hemolysins can be easily differentiated from homologous sheep hemolysins by the fact that the former do not act on ox cells, while the latter do. Friedemann [2] examined the so-called normal sheep hemolysins occurring in human sera and found them to be of the Forssman type. He introduced the name "heterophile" for such antibodies in general, a designation which has become widely accepted. Therefore the term Forssman antibody should be used only for anti-sheep bodies which fully correspond to the well-defined Forssman antigen in the guinea pig kidney or to similar tissue antigens.

Increase in the titer of sheep antibodies in human serum was observed by Hanganutziu [3] and Deicher [4] after injection of animal serum and by Paul and Bunnell [5] in cases of infectious mononucleosis. Mainly through the work of Davidsohn [6] and Stuart and co-workers [7] routine methods were introduced for differentiation of the three types of heterophile antibodies in human blood, namely the "normal" anti-sheep bodies, those found after serum injections, and the heterophile antibodies occurring in infectious mononucleosis.

Stuart and co-workers in cases of meningococcus meningitis complicated by serum sickness found heterophile antibodies, at least part of which behaved like the type of antibodies encountered in infectious mononucleosis. Sohier and co-workers [8] observed a titer of 1 : 160 for sheep cell agglutinins in the serum of a patient who apparently suffered from infectious mononucleosis. This agglutinin could be absorbed with guinea pig kidney and was present in the patient's serum only in the first of four tests made between the third and the twenty-ninth days after the onset of the illness. The authors

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drew attention to the fact that the patient had received treatment with a sulfonamide compound a few days before. It seems very unlikely that any correlation can be established between this medication and this very unusual serological finding. Warren,[9] quoting Sohier's observation, contended that the titer of normal heterophile antibodies (of the Forssman type) may be increased before or simultaneously with the appearance of the antibodies of infectious mononucleosis. Beer [10] questioned the usefulness of absorption of sheep agglutinins with ox cells. He compared the action of different types of heterophile antibodies on the blood of various animal species and concluded that at least part of the antibodies occurring after serum injection are identical with the normal anti-sheep bodies of the Forssman type.

Thus the differentiation of the three types of heterophile antibodies in human serum has become more involved, but their separate occurrence remains an established fact. In general, it can be stated that the titer of the normal heterophile antibodies is low, with a maximum for sheep cell agglutinins around 1 : 50, and that marked increase in titer is due to previous serum injection or to infectious mononucleosis. Few exceptions from this rule are recorded.

In 1931, Fischer [11] found that the serum of a patient who apparently had suffered from gonococcus septicemia contained a strong sheep cell agglutinin. No titer was given, nor were absorption experiments carried out. Paul and Bunnell [5] reported a high titer of heterophile antibody in the serum of a patient in the terminal stage of aplastic anemia with high fever. De Vries [12] saw a positive heterophile antibody reaction (1 : 128) in a case of scarlet fever and reported that Minkenhof had found "unexplained high titers in rubeola, tuberculosis and filariasis."

Bernstein,[13] stating that high titer heterophile antibody reactions not due to serum injection or infectious mononucleosis are "excessively uncommon," mentioned that parenteral administration of liver extract may produce titers as high as 1 : 1280. Bernstein has not yet reported this observation in detail.

It is surprising that increased titers of heterophile antibodies are not observed more frequently, because it has been shown that an ever increasing number of bacteria contain heterophile antigen. Among these bacteria are the Shiga bacillus and several pneumococcus and Salmonella types. Bailey [14] proved that not only injection of dead antigen preparations from such bacteria can increase the heterophile antibody titer in experimental animals, but that there is a relation between infection with *Past. lepiseptica* and increased heterophile antibody titer in rabbits. Bailey and Shorb [15] reported an increase of sheep hemolysins in the serum during the course of pneumonia. Hedén [16] saw the same in gonorrhea. Though he could not demonstrate heterophile antigen in gonococci, he quoted Bailey who found it, at least in one strain.

From these facts, it is apparent that there is some relation between heterophile antibody titer in human sera and infections. This relation is shown more clearly by the following case:

Case Report *

N. C., a 28-year-old white male, was admitted to this hospital on November 24, 1940. He had had urinary frequency, urgency and nocturia for 1½ years, after an upper respiratory infection, and for six months he had been complaining of abdominal pain in the right upper quadrant. Five days before admission he had taken castor oil and following that felt weak and had bloody stools. There was no history of injection treatment of any kind within many years. On admission he was severely anemic, his blood contained 1.9 million red blood cells and 32 per cent hemoglobin, the white blood count on November 25 was 6,600 leukocytes; the differential count showed 1 basophile, 5 staffs, 59 segmented polymorphonuclear neutrophiles, 31 small lymphocytes, 4 monocytes. There were occasional red and white blood cells in his urine. The diagnosis was bleeding duodenal ulcer and contracture of the bladder neck. The treatment consisted of blood transfusions, vitamins and Meulengracht diet. The patient's temperature varied between 99° and 103° and went to 106° on November 28. At this time a blood culture was taken and contained *E. coli*, 20 colonies per c.c. During the following night the temperature reached 107.5°. Signs of severe cystitis were present. Introduction of a permanent catheter brought relief. The white blood count on November 29 was 15,900 leukocytes, 16 staffs, 78 segmented polymorphonuclear neutrophiles, 5 lymphocytes, 1 monocyte. The urine contained staphylococci, streptococci, *Ps. pyocyanea* and *E. coli*. Sulfathiazole was given from November 28 until December 1. The patient's temperature came down to normal within a week. Blood cultures taken subsequently were sterile. Liver extract was given by injection for the first time on December 4. After his gastric condition had improved, the patient was transferred to the genito-urinary service where transurethral resection of the neck of the bladder was performed. He was discharged, very much improved, on January 15, 1941.

Serological Findings. On November 26, 1940, serum for a Wassermann test was obtained. The result of the examination was: Wassermann positive, Kahn and Kline tests doubtful. Repetitions on December 1, 4 and 12: Wassermann positive, Kahn and Kline tests negative. On December 31, 1940, and on April 10, 1941, when the patient was seen in the follow-up clinic, Wassermann, Kahn and Kline tests were negative.

The serum obtained on December 1 agglutinated the colon bacillus from the patient's blood up to a dilution 1:400. Among 10 strains of *E. coli* isolated from different cultures of the patient's urine none was serologically identical with the strain from the blood.

The serum specimen obtained on December 1 for a Wassermann test was first examined for sheep cell agglutinins on December 6 and gave agglutinations up to 1:1600 final serum dilution. The hemolytic titer was determined on December 10 and found to be 1:20000 (dilution of serum completely hemolysing an equal volume of 5 per cent sheep cell suspension in the presence of complement).

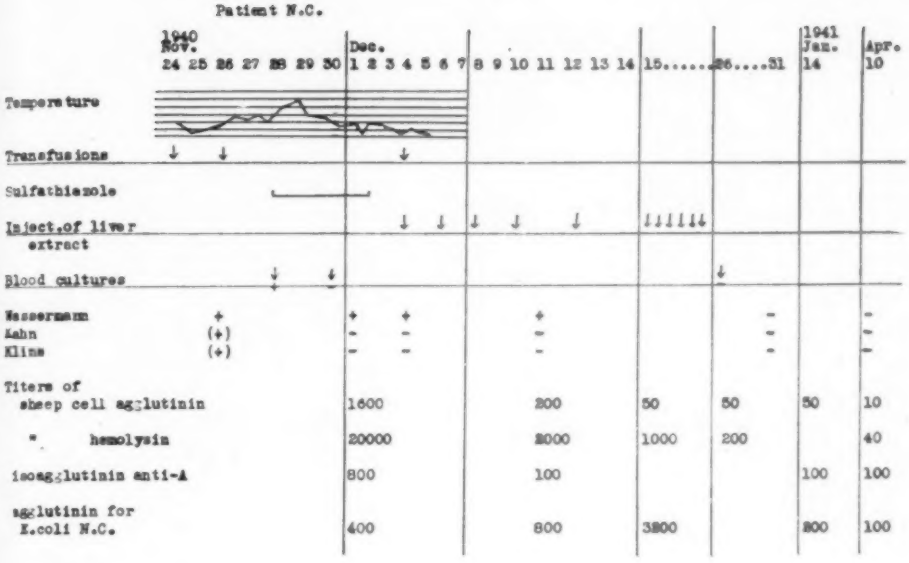
Serum obtained on December 11 was immediately examined for heterophile antibodies. It agglutinated sheep cells up to a dilution 1:200; the hemolytic titer was 1:2000. On December 15 the antibody content of the patient's serum had already reached the upper border of normal values and decreased further subsequently as may be seen from the chart (table 1).

The patient belonged to the blood group O. The α-agglutinin in the serum specimen of December 1 had a titer of 1:800. It decreased to 1:100 by December 11, remaining at this level throughout the observation.

On December 17 and 19 the two serum specimens obtained on December 1 and 11 were absorbed with 20 per cent suspensions of boiled ox cells and guinea pig kidney, using Davidsohn's technic (slightly modified). On this occasion it was noticed that the older serum specimen had lost three-fourths of its agglutinin and a large part of the

* Clinical data obtained by courtesy of Drs. H. A. Rafsky and A. Hyman.

TABLE I



hemolysin during storage in the ice box. However, the remaining antibodies (sheep cell agglutinin 1 : 400, hemolytic titer 1 : 2000) and the ones in the more recent serum specimen showed the same behavior, namely the heterophile antibodies could be absorbed with guinea pig kidney, but not with ox cells (table 2).

TABLE II

Serum N. C. 12/1

		Before Absorption	After Absorption: With G.P. Kidney	After Absorption: With Ox Cells	Serum D. W. 12/19 (infectious mononucleosis)	
					Before Abs.	Abs. with Ox Cell
Hemolytic titer (0.25 c.c. serum in dil., 0.25 c.c. 5% sheep cells, 0.25 c.c. complement 1: 10, 20′ at 37°)	Serum dilution:					
	1 : 250	c	o	c		
	1 : 500	c	o	c		
	1 : 1000	c	o	c		
	1 : 2000	c	o	c		
	1 : 4000	i	o	i		
	1 : 8000	o	o	o		
Sheep cell agglutination (0.3 c.c. serum in dil., 0.3 c.c. 1% sheep cells, after 10′ at room temp. centrifuge, shake and read)	Final dilution of serum:					
	1 : 25				+	(+)
	1 : 50				+	−
	1 : 100	+	−	+	+	−
	1 : 200	+	−	+	+	−
	1 : 400	+	−	+	+	−

c = complete hemolysis. o = no hemolysis. i = intermediate (partial hemolysis). + = agglutination. − = no agglutination. (+) = weak agglutination.

The titer for sheep cell agglutinins in the serum specimen of December 11 also diminished during storage in the ice box, and on January 7 was positive 1 : 50, weakly positive 1 : 100. Serum of a patient with infectious mononucleosis (D. W.) was obtained on December 19 and stored under fully identical conditions. The titer was not changed when examined last, more than six months after the specimen was taken.

TABLE III

Flocculation Test
(0.2 c.c. serum in dilutions, 0.2 c.c. alcoh. extract, 37° C. over night)

Serum-dil.	Sheep Cell	Ox Cell	Horse Cell	Guinea Pig Kidney Extract
	Serum N. C. 12/11			
1 : 2	+++	−	−	++++
1 : 4	+	−	−	+
1 : 8	+	−	−	+
1 : 16	−	−	−	(+)
	Serum D. M. 1/14 (infect. mononucl., heterophile antibody react.: 1 : 200)			
1 : 2	−	−	−	−
1 : 4	−	−	−	−
1 : 8	−	−	−	−
1 : 16	−	−	−	−
	Forssman-rabbit serum No. 20			
1 : 2	++++	−	−	+++
1 : 4	+++	−	−	+++
1 : 8	++	−	−	++
1 : 16	+	−	−	+

The flocculation test with alcoholic blood cell and organ extracts as described by Schiff [18] was done on January 15 with the serum specimen of December 11. There was flocculation with the extracts of sheep cells and guinea pig kidney, but none with ox cells and horse cells. The reaction was similar to one obtained with a Forssman rabbit serum. Serum of a patient with infectious mononucleosis, D. M. of January 14, which had a sheep cell agglutination titer of 1 : 200, gave no such flocculation (table 3).

TABLE IV

Hemolysis Inhibition Experiment

Rabbit serum No. 199 (after immunization with *E. coli* N. C.) three hemolytic doses; 0.25 c.c. 5% sheep cells; 0.25 c.c. complement 1 : 10; 0.5 c.c. of bacterial extracts in dilutions (24 hours' growth on agar slants washed off with 4 c.c. saline solution, heated at 60° C. for 30′, centrifuged, supernatant fluid used); 37° C. —30′.

Dilutions	Extract from *E. coli* N. C.	Extract from *E. coli* No. 1737
1 : 5	o	c
1 : 10	o	c
1 : 20	o	c
1 : 40	ao	c
1 : 80	wk	c
1 : 160	ac	c

c—complete hemolysis
ac—almost complete
wk—weak
ao—almost no hemolysis
o—no hemolysis.

Seven rabbits were immunized with the culture of *E. coli* obtained from the patient's blood, partly with organisms killed at 60° C., partly with suspensions of living organisms or both. Four of these rabbits showed an increase of sheep hemolysins after the immunization. It could be seen that all rabbits which had had no A substance in their serum and were injected with live organisms, had responded with formation of heterophile antibodies. In the hemolysis inhibition experiment an extract of the organisms showed strong inhibition, while an identical extract of a strain of *E. coli*, picked at random, failed to inhibit (table 4).

Discussion

In all likelihood *E. coli* had entered the patient's blood stream from the bladder wall. The regularity with which injection of living organisms of this strain caused an increase of sheep hemolysins in suitable experimental animals, and the inhibition of such hemolysins by an extract prepared from the culture, demonstrated the presence of heterophile antigen in this strain. Several authors had previously examined *E. coli* for heterophile antigen, but had obtained only negative results with all their strains. The heterophile antibody reaction of the patient's serum must be explained as the result of an immunization with the heterophile antigen contained in the *E. coli* strain as cultured from his blood. Infectious mononucleosis could be excluded from the clinical data. The patient had received neither a serum injection nor parenteral liver extract previous to the positive reaction. The antibodies could be absorbed with guinea pig kidney but not with ox cells, therefore they were of the Forssman type similar to the heterophile antibodies found in normal sera. The high titer of hemolysins in comparison to the titer of agglutinins is also characteristic of Forssman-like antibodies.

It has been stated repeatedly that sera from patients with infectious mononucleosis can be stored in the ice box for years without losing their antibody titer. The antibody encountered in this case partly disappeared from the specimens on standing in the ice box. Antibodies of such lability have been described before (by Kohn-Speyer [19]).

For the identification of heterophile antibodies of not very high titer, the flocculation test, as suggested by Schiff, proved to be of great value in this case. The increased anti-A titer at the height of the immunization effect reminds one of Davidsohn's observation of very high isoagglutinin titers in many patients with serum sickness.[20]

Non-specific Wassermann reactions, as found in our case, are known to occur in different infections, notably in infectious mononucleosis. There seems to be no direct connection between these reactions and the occurrence of the heterophile antibodies of infectious mononucleosis. The coincidence of such a Wassermann reaction with a heterophile antibody reaction of a different type is noteworthy but does not offer an explanation for its meaning.

The fact that heterophile antibodies appear faster and also disappear more quickly from the blood than bacterial agglutinins has been pointed out. This difference is striking in this case where both antibodies were produced by an infection with the same bacillus.

Summary

A strain of *E. coli* cultured from the blood of a patient with severe cystitis contained heterophile antigen. Following the bacteremia the patient's serum gave a positive heterophile antibody reaction (1 : 1600). The antibodies could be differentiated from the ones observed in serum sickness and in infectious mononucleosis, and were of Forssman type. They disappeared rather quickly from the patient's blood and vanished partly from serum specimens kept in the ice box, unlike the antibodies of infectious mononucleosis. The Wassermann reaction was positive for some time, and there was a temporary increase of isoagglutinins.

Conclusions

It is known from animal experiments that infection with bacteria containing heterophile antigen can increase the titer of heterophile antibodies in the serum. The same can happen in man. Though the increase in antibody titer is ordinarily of minor degree, it can become very marked. The quick disappearance of the antibodies from the blood and their lability in the specimen may account, at least in part, for the rarity with which heterophile antibody reactions of this kind are observed. The antibodies in such cases are of the same type as those encountered in normal sera, which makes it probable that there is a relation between the fluctuating titers of these antibodies and infections.

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THE TREATMENT OF DELIRIUM TREMENS WITH FARADIC SHOCK THERAPY; A NEW APPROACH BASED UPON THE PSYCHOBIOLOGICAL CONCEPT *

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DELIRIUM tremens is an acute alcoholic psychosis which usually follows a prolonged debauch, but which may also appear as an episode in the course of chronic alcoholism. It occurs in less than 10 per cent of all alcoholic admissions.[1] It is characterized by illusions, terrifying hallucinations, marked tremors and profuse perspiration. Usually it is preceded for several days by anorexia, restlessness and fear, but it may come on acutely. Kraepelin [2] stated that its duration varied from a few days to two weeks, but recent workers report that the average case recovers in four to six days.[3] Besides the typical cases, some run a shorter course (abortive cases) and some go into a subacute or chronic condition (Korsakoff's psychosis or "chronic alcoholic delirium"). The mortality in uncomplicated cases of delirium tremens is about 4 per cent, but it is as high as 25 to 40 per cent when the cases are untreated or when the delirium occurs in association with pneumonia or other infection.

There is no general agreement about the underlying mechanism of delirium tremens. Some believe that the mental symptoms are due to toxic changes in the cortical and ganglionic cells,[4] or to cerebral edema ("wet brain").[5] But most recent investigators claim that the histological changes in the brain are obscure in uncomplicated cases, and that the changes found do not differ from those seen in chronic alcoholism without delirium.[6] Also, the "wet-brain" theory now has fewer supporters. Results obtained with dehydration and spinal drainage have not been superior to those obtained with rehydration.[7] A few writers [8] still maintain that abstinence from alcohol is the chief causative factor of delirium tremens, but the majority of writers recommend abrupt withdrawal. Bowman, Wortis and Keiser [9] point out that the marked aversion toward food and alcohol in the prodromal period is due to acute gastritis and hepatitis and that abstinence is a result rather than the cause of the delirium. Since anorexia is so common in the prodromal stages, many now regard a sudden deficiency in vitamin intake as the cause. Keine, Streitweiser and Miller [10] urge the use of vitamin B_1, claiming that neither the toxic effects of alcohol nor its sudden withdrawal bring on delirium tremens.

Several workers [11] have recently reported that they were able to shorten the duration of delirium tremens with insulin and metrazol shock treatment.

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Steck [12] and Robinson [13] report that they have been able to shorten the duration of the delirium to an average of 2.5 days with insulin sub-shock therapy. Robinson believes that "toxic intermediate products due to deficient carbohydrate metabolism and deficient liver function produce the pathology and symptoms of delirium tremens and that the administration of insulin reëstablishes normal carbohydrate metabolism." At the Bellevue Hospital, Orenstein et al.[14] report that they have shortened the duration with subconvulsive doses of metrazol. They ascribe their results to direct stimulation of the central nervous system by the action of the metrazol.

Although many writers have suggested that psychogenic factors have an important bearing on delirium tremens, this important phase has been relatively unexplored. Jewett [15] believes that delirium occurs especially in those who are liable to mental and sensory hyperesthesia. Strecker and Ebaugh [16] point out that shadows in darkness increase fears and disorientation which accounts for patients being more disturbed at night. Bowman et al.[9] stress the need of considering the psychogenic factors, since fear is usually the primary effect of this condition. According to Fantus [17] the development of delirium "depends on (*a*) the severity of the toxemia or malnutrition, and (*b*) the constitutional and emotional stability of the patient at the time of illness," and that "patients under emotional tension may develop delirium from relatively slight causes."

Any acute toxic disturbance primarily affects the sensorium-intellect which in turn affects judgment, orientation and emotion. The resulting symptom-complex is known as delirium. This symptom-complex closely resembles the delirium which results from psychogenic disturbances. The emotional tone of delirium is usually that of anxiety, apprehension, or terror. Since most chronic alcoholics are constitutionally inferior or emotionally unstable, it is evident why delirium so often occurs in cases of severe intoxication. Since acute and unpleasant psychotic symptoms in the psychogenic psychoses are often terminated rapidly with shock treatment, the writer has sought to determine whether or not the duration of the psychoses which occur with alcoholism could also be shortened by the same method of treatment. The faradic shock treatments were administered in conjunction with the usual routine medical treatment.

Seventy-six patients under 55 years of age, diagnosed as having uncomplicated conditions of delirium tremens, were included in this study. These were selected from a total of 274 patients admitted for various forms of alcoholism on the Neuropsychiatric Service of the Minneapolis General Hospital. This unusually high proportion of delirium tremens admissions can be attributed to the large number of impending delirium tremens cases transferred from the city jail and the workhouse. Patients over 55 years of age were not considered in this study, in order to exclude the cases which might have irreversible brain damage from cerebral arteriosclerosis or advanced chronic alcoholism.

Method of Treatment

The routine medical treatment for all alcoholics with psychoses was as follows: (1) prompt withdrawal of alcohol; (2) 100 c.c. of 50 per cent glucose solution intravenously with 15 units of regular insulin in the more severe cases; (3) paraldehyde, chloral hydrate or other rapidly acting strong sedatives when necessary; (4) physical restraints when necessary; (5) fluids forced and 10 grains of sodium chloride t.i.d.; (6) 10 grains of brewers' yeast t.i.d., and 1 c.c. of cevitamic acid, subcutaneously, each day; (7) a high carbohydrate diet; and (8) an ounce of magnesium sulfate the first morning in the hospital. As in most charity hospitals, ideal treatment was not always practicable for financial reasons. Because of limited nursing help delirious patients were often placed in restraints. Strong sedation was not prescribed during the day unless the patient was extremely restless or disturbing to others. For the purpose of comparison in the present study the duration of the delirium was measured by the number of days strong sedation was required for restlessness and sleep.

Only a brief description of the apparatus and technic used in administering faradic shock therapy is given here, for a detailed account of these was presented in a previous paper.[18] One electrocardiograph electrode was applied to the forehead and another to the back of the neck. A series of 15 subconvulsive electrical shocks was given with a faradic current of one-half second's duration at intervals of one-half second. This current was produced by an induction coil energized by a six-volt dry cell battery, type A. The patient received an average current of about 10 milliamperes in each shock. A sinusoidal current may be used in place of the faradic current, but a higher amperage would then be required. Immediately following the series of electrical shocks an intravenous injection of pentothal sodium was given. Eight to 10 c.c. of a 5 per cent solution were required to produce general anesthesia for three to five minutes in chronic alcoholic patients. In a few cases sleep was not produced even with this large amount, but larger dosages were not given. Upon awakening, the patient was usually confused and poorly coördinated for only a few minutes. As the effects of the pentothal sodium wore off, the patient's apprehensiveness, hallucinations, and tremors diminished or left entirely. His intellectual faculties cleared and he remained in a relaxed condition. He was then in a more receptive state to receive reassurance and explanation of the cause of his mental disturbances. Two patients became more disturbed when given an insufficient amount of pentothal sodium solution (less than 6 c.c.) to produce relaxation. In these two cases, after more pentothal sodium was injected, complete relaxation followed. These shock treatments were repeated daily until all apparent symptoms of delirium disappeared. Some of the patients resisted the administration of the treatment, but after it was given they were grateful for the relief obtained and submitted more readily to following treatments if more were required. After each treatment the pa-

tient was not permitted to remain in bed, but was taken into the day room, encouraged to mix with other patients and to take an active part in occupational therapy. This procedure is considered an essential part of the treatment.

Many of the patients treated with faradic shock therapy did not receive their first treatment for two or more days after their admission to the hospital because of questionable diagnoses. The various types of acute alcoholic psychoses (pathologic drunkenness, abortive forms of delirium tremens, and delirium tremens), at their onset often do not lend themselves to precise clinical differentiation. If the condition in these doubtful cases became aggravated, and if it were permissible, faradic shock treatment was given.

Case Reports

Case 10. J. S., a male, aged 35 and single, had been emotionally unstable since childhood. His father and three brothers were heavy drinkers. The patient began to drink at 16 years of age. He had never been able to hold a steady job. He had been arrested 12 times for alcoholism and had had delirium tremens at least seven times. After his most recent arrest, he had been transferred to the hospital because he had become markedly disturbed at the city jail. As soon as he entered the hospital he begged for paraldehyde. He was seeing giraffes, monkeys, and lilliputians. He was given 3 drams of paraldehyde and 50 c.c. of 50 per cent glucose intravenously with 15 units of insulin. It was necessary to repeat the paraldehyde during the night. Because of his delirious and destructive behavior he was kept in restraint almost constantly, and was given 3 drams of paraldehyde three to four times daily, for four days. Since he did not show improvement, but continued to be restless and disturbed, on the fifth day he was given a faradic shock treatment with 10 c.c. of pentothal sodium, intravenously. Following this treatment his hallucinations disappeared and he remained quiet for three hours. Again he began to beg for paraldehyde. He became so disturbing to the other patients that he was given paraldehyde several times that afternoon and night. As the following day was Sunday, he did not receive shock treatment but he required paraldehyde three times that day. On Monday, the seventh day in the hospital, he was given the second shock treatment. From then on he required no further sedation during the day. He continued to improve after the second and third treatments, and was given chloral hydrate only at bedtime. After the fourth treatment he was no longer apprehensive or restless and he required no further sedation. Because he was such a difficult problem he was given a fifth treatment to insure against possible relapse.

Case 12. K. T., a male, aged 39, married three times, a college graduate and a successful business man, had been a periodic drinker for many years. In the year preceding admission he had had three attacks of delirium tremens. Each attack lasted three to four days. Prior to the present attack he drank from one to two quarts of whiskey daily for over a week. He then began to see animate objects on the wall and undertakers in his room. Because of his noisy and disturbed condition, the police were called and he was taken to the General Hospital late at night. He was placed in restraint, and given 2 drams of paraldehyde and 15 grains of chloral hydrate. Early in the morning he again became disturbed, and the same medication was repeated. Later that morning he was given a faradic shock treatment with 8 c.c. of pentothal sodium intravenously. After the treatment he showed marked improvement. He was discharged that same evening, since he appeared to be fully recovered and insisted on being discharged. When seen five months later, he vouched that he had not touched liquor since he left the hospital.

Case 17. C. B., a male, aged 40, and married, had been a heavy drinker since the age of 18. For many years his wife had threatened to divorce him because of his excessive drinking. Prior to admission, he drank from one pint to one quart of whiskey daily for six months. When he could not get whiskey he drank denatured alcohol or bay rum. Because of frequent intoxication he lost his job as a common laborer with the WPA. Shortly after this he was brought to the hospital in a delirious condition. He was placed in restraint and was given paraldehyde several times that night and the following day. The second morning he was given a faradic shock treatment with 10 c.c. of pentothal sodium each day for four days. After the first two treatments he was given chloral hydrate only at bedtime. He no longer had visual and auditory hallucinations after the second treatment. He remarked: "That treatment surely clears my head in a hurry—it is much better than that paraldehyde." He appeared to be fully recovered after the third treatment, but was given one additional treatment.

One month after his discharge he was still unemployed. He returned to the outpatient department for a nerve sedative. Two months later he became depressed because he could not obtain work. He again began to drink heavily. Four weeks later he again became delirious and was readmitted to the hospital. He was given 50 c.c. of 50 per cent glucose intravenously with 15 units of insulin and one-quarter grain of morphine sulphate. After two hours of sleep he became so disturbed and noisy that he was given 2 drams of paraldehyde and 15 grains of chloral hydrate and placed in restraint. The following day he refused faradic shock therapy because he was apprehensive and afraid to take it. Because of his attitude, sedation was purposely withheld that day. He continued to be so extremely restless and disturbed that 3 drams of paraldehyde were required every four hours on the third and fourth days. His hallucinations and delusions persisted. He saw strange animals and believed that some men wanted to kill him. On the fifth day, after being told that he could have no more paraldehyde, he consented to receive faradic shock treatments. After the first treatment his hallucinations disappeared. He confessed that he should have taken the treatment when it was first offered for it helped him greatly. After the second treatment he remarked: "Don't give me any more paraldehyde—it only makes me more dopey and confused." He became coöperative, sociable, neat in appearance, and slept without sedation. After the third treatment he was symptom free.

Case 19. G. K., a male, aged 43 and single, had been an alcoholic for 23 years. He was admitted to the hospital on September 1, 1940, in his third attack of delirium tremens within two years. He frequently begged for paraldehyde, but refused the faradic shock treatment. Because of his violent and disturbing behavior he was given paraldehyde every day during his 10 day stay in the hospital. Four months later, following another debauch, he was readmitted in a delirious state with marked tremors, profuse perspiration and terrifying hallucinations. He was given 3 drams of paraldehyde on the night of admission and five times the following day. His condition grew worse. On the second morning he was given a faradic shock treatment with 8 c.c. of pentothal sodium. His hallucinations disappeared after the shock treatment. After his noon meal he remarked that it was the first good meal he had had in a week. Toward evening he again became restless, continuously paced the floor, but the hallucinations did not return. At night he was given 3 drams of paraldehyde for sleep. The following morning, after the second faradic shock treatment, all his symptoms disappeared and he required no further sedation. He was kept in the hospital five more days for further observation and to provide him with another fresh start.

Case 26. K. H., a male, aged 31, single, a meat cutter, had been a heavy drinker since the age of 17. After an alcoholic debauch of six weeks' duration he stopped drinking abruptly so that he could return to work. Three days later he began to see

lions, prairie chickens, and other animals. He became so frightened and excited that the police were called at an early hour to take him to the hospital. He was given 3 drams of paraldehyde, but he again became markedly disturbed three hours later. His excitement continued until he was given a faradic shock treatment with 10 c.c. of pentothal sodium. Following this treatment he remained calm, his hallucinations left, and he required no further sedation. The second morning he was quiet and rational, but slightly tremulous. After the second faradic shock treatment he showed no further symptoms.

Case 28. J. F., a male, aged 42 and married, had been committed for alcoholic psychosis to the St. Cloud Veterans' Hospital on three previous occasions. For three weeks before his admission to the Minneapolis General Hospital he drank one quart of whiskey every day and took two to three ounces of paraldehyde every night for sleep. Three days before his admission he stopped drinking abruptly. He was taken to the hospital in a delirious condition. He was given 3 drams of paraldehyde that night and three times the following day. As this failed to quiet him, he begged for more. The second morning he was given a faradic shock treatment with 10 c.c. of pentothal sodium. Greatly improved after the treatment, he said: "Yesterday I would have drank anything that I could lay my hands on, but now I swear I will never drink again." No further sedation or shock treatment was necessary because he showed no further symptoms. He was kept in the hospital, however, three more days for further observation.

Case 30. D. F., a male, aged 37, single, a garage mechanic, had been a periodic drinker since the age of 20. After drinking heavily for 10 days, he was taken to a private hospital in a disturbed condition. He was transferred to the Minneapolis General Hospital the following evening because he became so belligerent and violent. He thought men were threatening him with knives and saw some staring at him from the ceiling. He refused paraldehyde that evening because of nausea and remained extremely restless throughout the night. The following morning, after receiving a faradic shock treatment with 10 c.c. of pentothal sodium, he showed much improvement. In the afternoon his hallucinations returned, and he again became noisy. That evening he was given paraldehyde and chloral hydrate twice. The following morning, after the second faradic shock treatment, he showed no further symptoms. He told the nurses and other patients how much the shock treatment had helped him. He was kept in the hospital two more days for observation.

Case 31. A. T., a male, aged 36, single, and a bartender, drank heavily periodically for 18 years. He had had delirium tremens one year previously. He drank more than one quart of whiskey daily for six weeks until five days before admission to the hospital. Visual hallucinations appeared one day before his admission. On admission he was tremulous, fearful and excited. He slept very little that night, although on two occasions he received 2 grains of phenobarbital and $\frac{1}{100}$ grain of hyoscine hydrobromide subcutaneously. The following morning he was seen picking imaginary spiders off his blanket. He also complained that a little negress was throwing lice at him. Although oriented as to time and place, he saw scores of penguins as large as sheep. He was given a faradic shock treatment with 10 c.c. of pentothal sodium. Two hours after the treatment he was not so restless, but he was again confused. When asked where the penguins were he hunted about the room, remarking: "That is strange . . . I saw them here before." In the afternoon, although he was less disturbed, he again saw the penguins but they were smaller in size. Some were small enough to crawl through cracks. Later in the same afternoon, after a second treatment, he again improved. He played checkers and was greatly pleased with the relief the treatment gave him. In the evening, however, he again became restless and tremulous. He was given 2 grains of sodium luminal intravenously and $\frac{1}{100}$ grain of hyoscine subcutaneously for sleep. The following morn-

ing, after the third faradic shock treatment, he fully recovered. Later in the day he remarked: "I really thought that I saw penguins yesterday. I must have been insane. . . . I sure feel fine now." The change in his behavior and attitude was remarkable. He was not discharged until two days later, however, so that he could be provided with a fresh start.

Summary of Results

Since the use of faradic shock therapy in the treatment of delirium tremens was considered as an experimental procedure, the hospital regulations did not permit us to force its use on unwilling patients. Written consent was frequently denied to us because the nature of such a request seemed to imply to many that the treatment entailed certain dangers. Consequently, we were unable to treat every other admission of delirium tremens with this treatment.* As stated above, all patients, whether given shock treatment or not, received the same routine medical treatment. The group which received faradic shock therapy (table 1) includes those who gave consent and those who were in no condition to give consent and whose relatives could not be reached. The group not treated with faradic shock therapy (table 2) includes those who strongly objected to the shock treatment and those who, on admission, had such mild symptoms that they were at first regarded as having abortive forms but later were considered as milder forms of delirium tremens, since their symptoms did not abate promptly with the usual routine medical treatment. It is obvious, therefore, that most of the severe cases were among the first group.

Thirty-three cases of delirium tremens in Group I were given faradic shock therapy in addition to the routine medical treatment, and 43 were given only the routine medical treatment (Group II).

Among the 76 patients reported in this paper there was only one death. This patient did not receive faradic shock treatments. He showed no evi-

* Beginning January 1, 1941, the writer obtained permission from the Minneapolis General Hospital administration to administer faradic shock therapy to patients with delirium tremens without obtaining their written consent. A better controlled statistical evaluation was thereby made possible. To determine the relative effectiveness of paraldehyde, intravenous barbiturates, and faradic shock therapy with intravenous pentothal sodium, all uncomplicated cases under 55 years of age on admission were assigned in alternation to three groups. The interns were instructed to prescribe strong sedation to all patients in the three groups only when it was urgently required. Whenever intravenous medication failed to quiet the patients in the second and third groups, 3 drams of paraldehyde were given one-half hour later. Thirty patients were admitted from January 1 to July 1, 1941, so in each group there were 10 patients. The 10 patients in the first group who received paraldehyde recovered in an average of 3.7 days, the 10 patients who received intravenous barbiturates (pentothal sodium or sodium amytal) in 2.7 days, and the 10 patients who received faradic shock with intravenous pentothal sodium in only 1.9 days. The writer believes that the results in the first group were lower than the average of 5.0 days reported in this paper because the paraldehyde was withheld more stringently. The second group responded still more promptly, indicating that intravenous barbiturates further shorten the duration of the delirium. In the third group the duration was shortened from the average of 2.2 days reported in this paper because in all cases the faradic shock treatment was administered on the first morning of admission. These results indicate that intravenous barbiturates shorten the duration of delirium tremens, but when used in conjunction with faradic shock treatment the duration of the delirium is further shortened.

dence of infection until 36 hours after admission, when his temperature began to rise. He expired from pneumonia shortly afterwards.

In only one case was a patient treated twice on the same day with faradic shock. There is no reason why this treatment should not be given twice daily if the patient shows need for it. This may further shorten the duration of the illness.

TABLE I

Group 1, Delirium Tremens Treated with Faradic Shock Therapy

Case No. and Name	Sex	Age	Days in Hospital Before Faradic Shocks Given	Days Faradic Shocks Given	Days Strong Sedation Required After 1st Treatment	Days Strong Sedation Required in Hospital
1. N.N.	M	33	1	2	1	2
2. P.H.	M	39	1	5	4	5
3. F.H.	M	39	2	1	0	2
4. S.B.	M	39	2	2	0	2
5. N.H.	M	35	2	2	1	3
6. R.F.	M	34	1	1	0	1
7. E.S.	M	43	2	2	0	2
8. E.C.	M	38	1	1	0	1
9. G.B.	M	48	1	1	0	1
10. J.S.*	M	35	4	5	4	8
11. T.T.	M	47	3	2	1	4
12. K.T.*	M	39	1	1	0	1
13. R.H.	M	36	2	2	0	2
14. P.H.	M	39	2	2	2	4
15. G.J.	M	40	1	2	0	1
16. E.B.	F	39	2	1	0	2
17. C.B.*	M	40	2	4	0	2
†			5	3	1	6
18. P.M.	M	41	1	1	0	1
19. G.K.*	M	43	1	2	1	2
20. S.E.	M	34	1	1	0	1
21. T.T.	M	47	1	2	0	1
22. T.F.	M	34	1	3	0	1
23. F.C.	F	40	2	6	3	5
24. S.T.	M	46	1	3	0	1
25. D.L.	F	41	1	1	0	1
26. K.H.*	M	31	1	2	0	1
27. L.L.	F	40	2	1	0	2
28. J.F.*	M	42	1	1	0	1
29. A.D.	F	48	1	2	0	1
30. D.F.*	M	37	1	2	1	2
31. A.T.*	M	36	1	2	1	2
32. C.B.	M	44	3	3	0	3
33. E.B.	M	43	1	2	0	1

* See case report. † Second admission.

There was very little difference in the ages of the two groups. The average age in Group I was 38.5 years, and in Group II it was 40.5 years.

The average number of daily shock treatments administered was 2.2. A few patients received an extra treatment after all symptoms disappeared to make certain that recovery was complete.

The mean number of days strong sedation was required in Group I was 2.21 with a standard deviation of 1.66, as compared with the mean of 5.05

days with a standard deviation of 3.33 in Group II. The difference of the means was 2.84 ± 0.59. The ratio of the difference to the standard error of the difference was 4.82. Therefore, the probability of the difference arising through chance alone would be extremely small.

The average number of days before administration of the faradic shock therapy was 1.6, for several did not receive this treatment for two or more days after their hospital admission. It is quite probable that the duration of the delirium could have been shortened if all the patients in Group I had been given their first treatment on admission.

TABLE II

Group 2, Delirium Tremens Treated without Faradic Shock Therapy

Case No. and Name	Sex	Age	Days Strong Sedation Required in Hospital	Case No. and Name	Sex	Age	Days Strong Sedation Required in Hospital
1. H.L.	M	39	4	23. S.T.	M	45	6
2. G.M.	M	27	2	24. J.L.	M	35	10
3. M.B.	M	43	5	25. P.C.	M	38	4
4. M.M.	M	33	13	26. H.L.	M	39	5
5. L.H.	M	49	3	27. B.J.	M	42	4
6. C.B.	M	45	10	28. T.F.	M	35	5
7. E.S.	M	50	5	29. S.H.	M	38	9
8. J.C.	M	35	5	30. E.B.	F	39	9
9. A.K.	M	49	3	31. G.B.	M	41	3
10. D.E.	M	39	3	32. D.H.	M	42	4
11. L.H.	M	50	5	33. G.H.	F	34	4
12. A.B.	M	46	4	34. B.S.	F	34	2
13. M.W.	F	32	4	35. S.B.	M	42	19
14. E.O.	F	29	4	36. E.S.	M	41	2 (died)
15. H.L.	M	39	4	37. P.F.	M	45	3
16. G.A.	M	46	2	38. R.A.	M	32	2
17. S.B.	M	42	3	39. C.B.	M	42	4
18. D.S.	F	35	3	40. B.P.	M	49	7
19. L.J.	M	32	3	41. G.D.	M	47	3
20. W.C.	F	31	3	42. J.C.	M	36	2
21. G.K.	M	43	10	43. E.Y.	F	46	6
22. J.C.	M	35	6				

The average number of days strong sedation was needed after the first faradic shock treatment was only 0.6 days. This low figure strongly indicates the effectiveness of the treatment. Only six, or 17 per cent of the 33 patients, of those treated with faradic shock reached or exceeded the median number of days strong sedation was required in those who received only the routine medical treatment.*

* Four cases of pathologic drunkenness recovered promptly after they were given one faradic shock treatment. Two cases of Korsakoff's psychoses were also treated with faradic shock treatment. They developed delirium, extensive confabulation and peripheral neuritis after several months of heavy drinking. The symptoms of delirium disappeared after two faradic shock treatments, but they continued to be mildly confused at night for several days. The peripheral neuritis, however, persisted for several months. In addition to these cases, other forms of toxic psychoses treated with faradic shock treatment will be discussed in a future report.

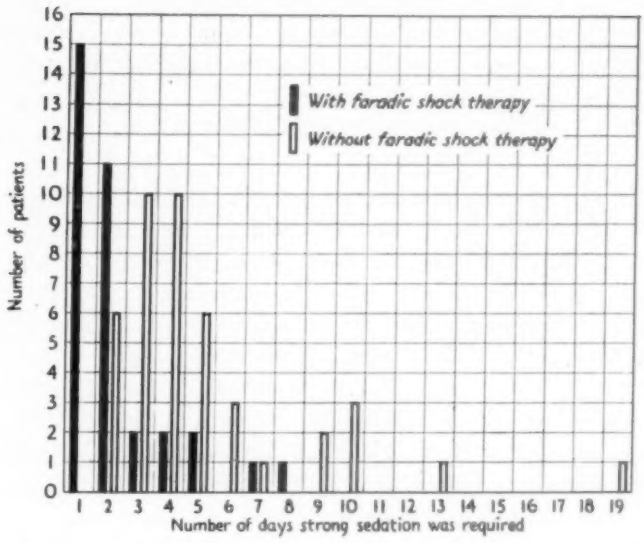

FIG. 1. Graphic representation showing the number of days strong sedation was required by patients with the symptom-complex of delirium tremens. Forty-three cases were treated with routine medical treatment (white bars), and 33 cases were treated with the same routine treatment together with faradic shock therapy (black bars).

COMMENT

As early as the first half of the nineteenth century, Esquirol [19] considered alcoholism as a symptom rather than a cause of the psychosis. Janet [20] commented that the " patients themselves have not been alcoholics all their lives, but they were already sick persons before they took to drink." In a searching study of 65 cases he found that over 50 of these exhibited multiform neuropathic symptoms before they took to drink. In a recent study of 97 cases Davidoff and Whitaker [21] corroborated his observations. Alcohol furnishes the easiest means of escape from disagreeable reality, for it temporarily blurs or obliterates unpleasant situations. Unfortunately, however, in many cases habituation ultimately follows.

Besides the psychogenic factors, several physiologic conditions also contribute to the etiology of delirium tremens. Many in the past considered sudden withdrawal of alcohol the cause, but now only a few consider it an important factor. In all forms of drug addiction, the physiologic processes of the organism gradually become accustomed to the drug. Therefore, a sudden abstinence produces a temporary dysfunction of the autonomic nervous system. The resulting physiologic disturbances are responsible in part for such symptoms as restlessness, apprehensiveness and anxiety. Hence, a sudden withdrawal must be considered as an important contributory factor in the production of delirium.

Another contributory factor is malnutrition. This condition often occurs in the course of a prolonged drinking bout. Since the rôle of vitamins has recently come to the foreground, some workers now maintain that avi-

taminoses are the cause of the delirium. Although subvitaminoses may often occur, there is, as yet, no conclusive evidence that vitamin deficiency alone causes delirium tremens. In a recent study by Rosenbaum et al.,[22] it was found that once the disorder starts, vitamin therapy does not seem to shorten the illness. Nevertheless, all patients in this study were treated for malnutrition.

Since all traces of alcohol leave the body in less than 24 hours, some hold that delirium tremens is not caused by the toxic effects of the drugs alone. It is well known, however, that alcoholic intoxication impairs judgment and orientation by the involvement of the higher centers (sensorium-intellect). These changes secondarily affect the emotions-will field and the autonomic nervous system which creates emotional excitement and fear. As early as 1886, Blandford [23] stated that " the toxic effects of alcohol reduce the nerve centers to such an unstable state that the slightest thing such as an accident, grief, anxiety or mental shock upsets the balance." Today these same conditions are recognized as precipitating factors in psychogenic psychoses, or in delirium tremens, or following a prolonged drinking bout.

Therefore, delirium tremens is not an isolated organic disorder, but rather a symptom-complex resulting from psychogenic as well as physical causes. Mental disturbances arising from psychogenic or physical causes show themselves chiefly through alterations of physiologic functions (autonomic nervous system dysfunction). Objective symptoms such as perspiration, anorexia, tremors, and vasomotor reaction which occur in delirium, arise from difficult life-situations, toxic-organic processes, or both. Thus, it is necessary to regard the human organism as an integrated unit. Fortunately, this concept is gradually replacing the dualistic view that mind and body are separate entities. It is bringing about a better understanding of how disturbances of the personality may result from psychologic or toxic-organic causes or both (figure 2). With this consideration the treatment of delirium tremens may be carried out more effectively.

Summary

Although there is no specific treatment for chronic alcoholism, the symptom-complex of delirium tremens is curable. In Osler's textbook [24] appeared a statement: " Delirium tremens is a disease which, in a large majority of cases, runs a course very slightly influenced by medicine." Although many may still hold this belief, observations of the recent investigators do not support this view. A conspicuous difference occurs in the mortality rates in the places where the cases are poorly treated and where adequate supportive and protective therapy is provided.

Although sudden withdrawal of alcohol often produces dysfunction of the physiologic processes in individuals whose organism has become habituated to the drug, the writer concurs with the majority in advocating this method of treatment. Practically all chronic alcoholics intend to " taper off " of their own accord, but they usually fail. It is poor medical practice

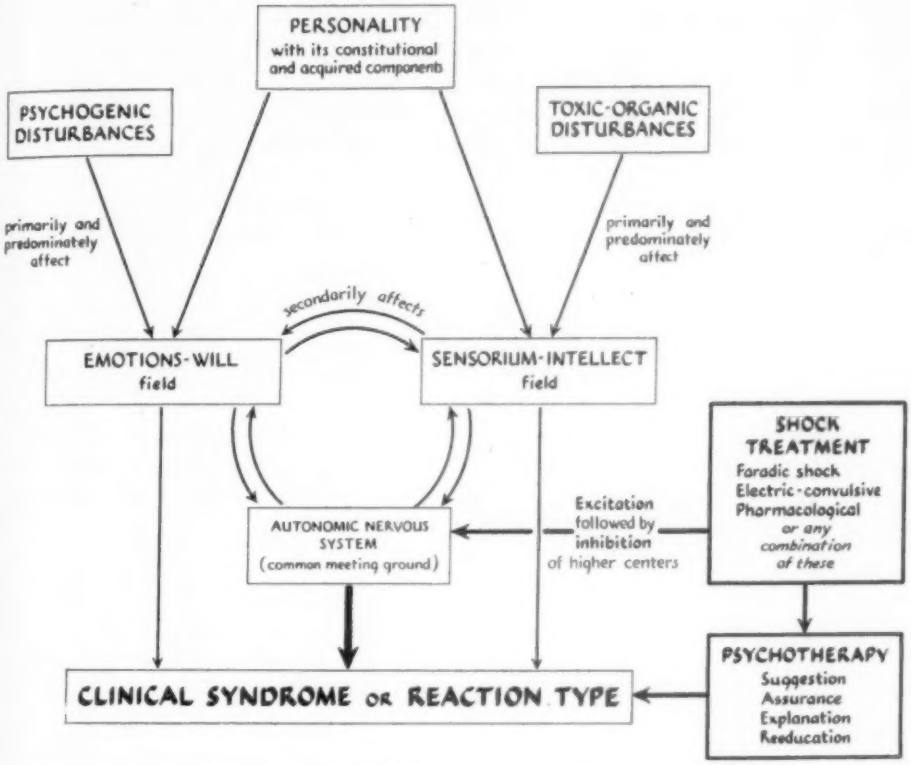

FIG. 2. Scheme showing how psychogenic or toxic-organic disturbance may affect the physiological processes and produce similar symptoms. If the psychogenic disturbances are not systematized and if the toxic-organic changes are not irreversible, shock treatment used in conjunction with psychotherapy may remove the psychotic symptoms by breaking the vicious circle.

for a physician to prescribe gradual withdrawal because it gives the patient professional sanction to a procedure which is fraught with danger. The patient and his relatives are led to believe that such a procedure is necessary and proper. Gradual withdrawal frequently prolongs and at times aggravates the condition.

Supportive and protective measures are essential in the treatment of delirium tremens. The various supportive measures necessary to maintain the vital functions and support the strength of the patient have been already described. The procedures used in this study are similar to those employed at the Bellevue Hospital [25] and at other leading centers.

The protective measures, chiefly physical and chemical restraints, were used to avoid accidental injuries and to prevent exhaustion. Paradoxical as it may sound, these measures, although essential, often prolong or aggravate the condition. Particularly at night, it was often necessary to use physical restraints for violent and disturbed patients, even though such methods often provoke constant struggle which causes further excitement and exhaustion. Since the action of sedative drugs on these patients is uncer-

tain, the application of restraints as a safeguard was often necessary, for without them constant vigilance would be required, but this is not practical in a general hospital because of the expense involved. Individual nursing care would be ideal, for the application of restraints would not be so often required. Continuous tub baths are far superior to the use of physical restraints, but as in most other general hospitals such equipment was not available. Sedative packs were not used for they also tend to increase the excitement by the restraint involved.

The use of chemical restraints presents as difficult a problem as that of physical restraints for they also are easily subject to abuse. The most satisfactory sedative used to produce sleep and prevent exhaustion in delirious patients is a quickly acting and rapidly eliminated drug. Since these patients often remain wide awake, in spite of heroic administration of hypnotics, it is evident that slowly eliminated drugs which accumulate in the system are contraindicated, for their toxic action may prolong and aggravate the condition.[26] According to Jewett,[15] the mortality was reduced more than half when he abandoned their use. Paraldehyde, the most popular drug used in the treatment of delirium tremens, was used most frequently by us. It is not an ideal sedative. Since it is closely related to ethyl alcohol it also irritates the stomach, produces "hangover" effects, induces delirium, and is habit forming. It was not given rectally for it is rarely retained by excited patients. Some advise against the use of paraldehyde for it often increases excitement.[27] Intravenous barbiturates are far superior, for their use eliminates most of these undesirable effects. The hypnotic effect is more certain, and the action and elimination are more rapid. Their administration entails no danger if one is fully informed about their pharmacologic characteristics. Several writers[28] have claimed good results with intravenous sodium amytal in controlling patients with delirium tremens, but the duration of its action in the excited patients has been so brief that it has not enjoyed a wide use.

In this study intravenous pentothal sodium was used exclusively for sedation following excitation with the series of electrical shocks because it is one of the most rapidly acting and eliminated drugs in the barbiturate series. Since its after effects are very transitory, the patient was in condition to receive psychotherapy soon afterwards.

Since delirium tremens generally has been considered as a purely toxic-organic disturbance, insufficient attention has been given to its psychogenesis. The personality with its constitutional and acquired components must be considered, as well as the various physical factors which contribute to its origin. Although in recent years several writers have pointed out the importance of considering the psychogenic factors, most therapists have continued to treat delirium tremens as a physical disease rather than as a psychobiologic reaction type.

Shock treatment does not change the preëxisting personality of psychotic individuals, but it usually removes unpleasant psychotic material if it is of

rather recent origin.[29] The same appears to be true in patients with delirium tremens. Shock treatment promptly relieves them of their acute mental symptoms and provides them with a fresh start, but it does not alter their underlying constitutional make-up. It is too early to determine whether faradic shock treatment may defer some from further drinking, but it appears quite likely that by interrupting the vicious circle at the onset acute mental disorders may be prevented from merging into more chronic forms.

Since the symptom-complex of delirium tremens is the result of psychogenic as well as physical conditions, it is logical to conclude that both of these conditions should be treated. By using faradic shock therapy, an apparently safe, effective, and inexpensive method of bringing about a quick relief of acute psychotic symptoms, together with the accepted routine medical treatment, the underlying psychogenic and physical factors are simultaneously treated. The duration of the illness was shortened to less than half the usual time by this procedure. Consequently, the danger of physical complications was also lessened.

Conclusions

The symptom-complex of delirium tremens results from psychogenic as well as physical conditions. The contributory factors are (*a*) the personality with its constitutional and acquired components, (*b*) the toxic effects of alcohol, (*c*) malnutrition, and (*d*) sudden withdrawal of alcohol. The precipitating factor may be an emotional shock, injury, or infection.

The routine treatment has been directed largely toward supportive measures, but the basic considerations of the psychopathology have been largely neglected. Experience has shown that the necessary "protective" measures (chemical and physical restraints) often aggravate or prolong the condition. Faradic shock therapy promptly removes the acute psychotic symptoms in most cases and, therefore, lessens the need of these undesirable protective measures.

Seventy-six cases of delirium tremens were given the same routine medical treatment. Forty-three of these, receiving only the routine treatment, required strong sedation for an average of 5.0 days. Thirty-three, receiving faradic shock therapy in addition to the routine treatment, required strong sedation for an average of 2.2 days.

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CARDIO-PERICARDIOPEXY; THE SURGICAL TREATMENT OF CORONARY ARTERIAL DISEASE BY THE ESTABLISHMENT OF ADHESIVE PERICARDITIS *

By Samuel Alcott Thompson, M.D., F.A.C.S., and Milton J. Raisbeck, M.D., F.A.C.P., *New York, N. Y.*

Coronary arterial disease is an ever changing process during the development of which the occlusive process is opposed by the formation of collateral anastomoses. When the adjustments within the heart are sufficient to compensate for the disease process, no symptoms occur, but when a discrepancy exists between the myocardial demand and the coronary supply, the resulting myocardial ischemia is responsible for the clinical syndromes of angina pectoris, congestive failure and myocardial infarction. The coronaries may be completely occluded without infarction or myocardial fibrosis if the development of the collateral circulation keeps pace with the occlusive process. This conception relates particularly to the mechanical effects of the disease, but these effects are the same regardless of the variations in the underlying etiology. The changes in the myocardium depend solely upon the extent and duration of the relative ischemia and not upon the manner in which the ischemia is produced.

The limit of adjustment between blood demand and supply, which has been called the coronary reserve, may be exceeded by an increase in the myocardial demand or a decrease in the coronary supply.

Rationale of Surgery

The rationale of surgery in the treatment of coronary arterial disease is to decrease the myocardial demand or increase the coronary supply, and has to do with operative procedures upon (1) the sympathetic nervous system, (2) the thyroid gland, and (3) upon the heart itself.

Operations upon the sympathetic nervous system interrupt the cardiosensory and motor pathways. This prevents the conduction of impulses responsible for painful sensations and possibly for spastic contraction of the coronary arteries. Spasm of the coronary arteries alone may lead to angina or, superadded to disease of an artery, may lead to myocardial infarction.

The operations usually consist in the removal of the upper four or five thoracic and the lower cervical afferent and efferent ganglia, or the nerves of these ganglia. Raney [38] reported a series of cases in which he severed only the motor nerves entering these ganglia, on the theory that the presence of

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disease reverses the normal physiology and the motor nerves then contract rather than dilate the coronary arteries. The validity of this theory is not established as the operation was performed only upon one side, but because of his reported low mortality and good results, the procedure appears to deserve a further trial. Injection of alcohol into these ganglia and the vertebral nerves, in our experience, has brought only temporary relief. Two of the patients in our series had received injections on two different occasions.

Total removal of the thyroid gland in coronary arterial disease was performed with the idea of reducing the metabolic rate and thereby reducing the myocardial demand to the level of a decreased coronary supply. This has been beneficial in some instances, but in general it has not stood the test of time. For this reason, and because of its high mortality, it is not considered a satisfactory procedure.

Grafting tissue onto the myocardium produces a collateral circulation in two ways: (1) intracardiac, by stimulating an increase in the size and function of the collateral channels which are already present in the heart; and (2) extracardiac, by the formation of new channels from the grafted tissue to the myocardium. This grafted tissue should have, or be capable of producing and maintaining a satisfactory blood supply. This additional blood supply augments the decreased coronary supply, and the myocardial ischemia is overcome not by eliminating coronary arterial spasm and not by decreasing the myocardial demand, but by increasing the actual blood supply to the heart. This comparatively recent principle in the treatment of coronary arterial disease, first applied to a human being by Beck,[2, 3] has been sufficiently demonstrated from experimental and clinical evidence to be physiologically sound. The tissues which have been used as grafts are muscle, omentum, lung and pericardium.

In cardio-myopexy, as developed by Beck, the epicardium is mechanically removed by a burr, and a portion of the pectoralis muscle is partially resected and applied to the denuded myocardium and pericardium. This operation is one of major proportions and must be limited to patients who are in condition to withstand major operative procedures. There is a certain operative mortality in patients with coronary disease, no matter what or how simple the operation.

In cardio-omentopexy, as developed and first performed by O'Shaughnessy,[35, 36, 37] the left pleural cavity is opened and a portion of omentum is brought up through a small incision in the diaphragm. The pericardium is opened and the epicardium is covered with an irritant salve. The omentum is then attached to the edges of the pericardium. The reaction produced by the salve causes the omentum to become adherent to the myocardium. This operation also is one of major proportions.

Cardio-pneumopexy has been performed upon two patients by O'Shaughnessy without relief of the symptoms.

The ability of the pericardium to serve as the source of a collateral cir-

culation has been known for some time and as a result of animal experimentation it was definitely recommended for such use in 1932 by Hudson, Moritz and Wearn.[22] Since that time other investigators have demonstrated the effectiveness of the pericardium as a source from which to develop a collateral circulation. O'Shaughnessy performed the first operation in which the pericardium was used as the source of the collateral circulation. Beck also reported a patient with congestive failure in whom he inserted powdered beef bone into the pericardial sac.

The blood supply of the pericardium is abundant (figure 1). It receives branches from the aorta, from the internal mammary, from the esophageal, from the phrenic, from the bronchial, from the mediastinal, and from the coronary arteries themselves. While these branches are normally small they, nevertheless, constitute a rich source for collateral communication with the coronary arteries.

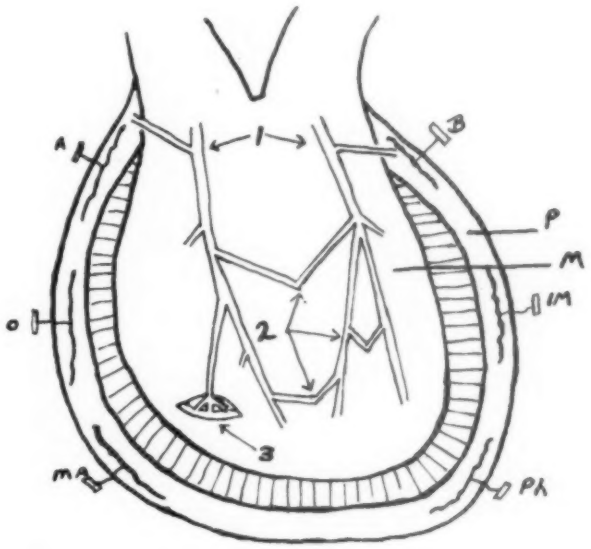


FIG. 1. This diagram illustrates the normal coronary artery anastomosis: (1) Extracardiac anastomotic branches to the pericardium. (2) Intercoronary anastomoses between the main coronary arteries. (3) Intracardiac anastomoses between branches of the same coronary artery.

The blood supply of the pericardium is also illustrated; the branches received are from the: B, bronchial; IM, internal mammary; Ph, phrenic; MA, mediastinal; O, esophageal; A, aortic; P, pericardium; and M, myocardium.

EXPERIMENTAL EVIDENCE

Contrary to the general belief, adhesive pericarditis is not readily or easily produced by mechanical trauma or by a host of chemical irritants. In a series of animal experiments we demonstrated the ability to produce adhesive pericarditis regularly and graft the pericardium on to the epicardium by the introduction of sterile talc powder (hydrous magnesium silicate) into

the pericardial sac.* The powder produces a foreign body reaction, characterized by a fibrinous pericarditis, with little or no fluid formation. As early as 18 hours after the introduction of the powder the pericardium becomes adherent to the epicardium at the site of insertion. After one week the two surfaces are firmly adherent, and after four weeks the pericardium and epicardium are fused as one layer of tissue. The presence of blood vessels from the pericardium to the epicardium was demonstrated at subsequent operations when bleeding was observed from both tissues when the two layers were separated. Also microscopic sections of injected specimens demonstrate the presence of blood vessels going from one tissue to the other (figures 2 and 2A).

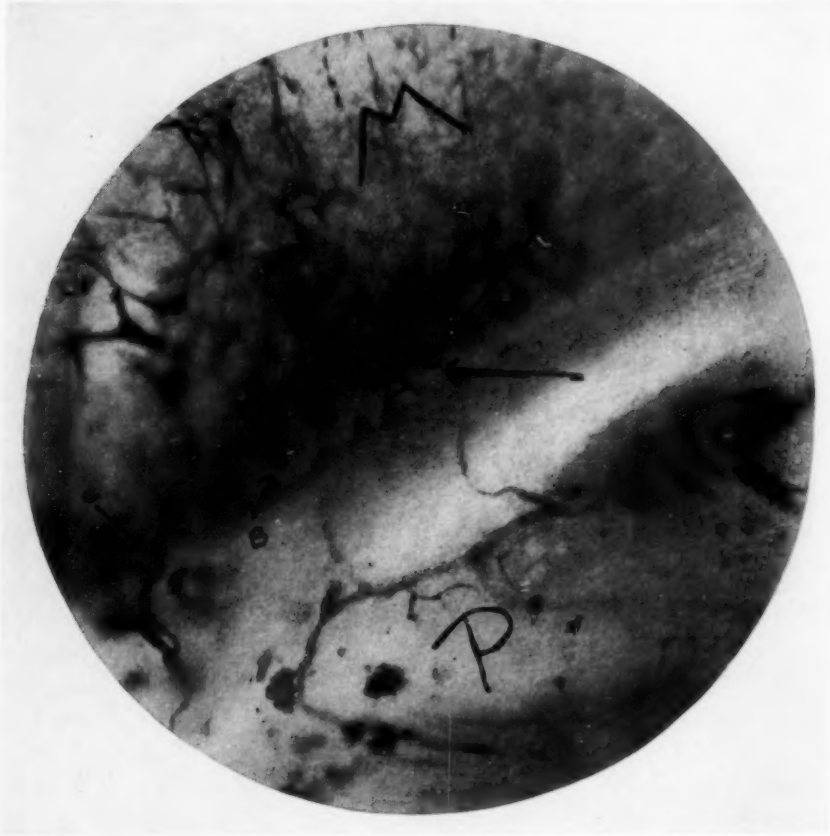


FIG. 2. Photomicrograph (low power) of a section of a dog's heart. Adhesive pericarditis was produced and this was followed by ligation of the left descending branch of the coronary artery. The dog was later sacrificed and the heart injected with India ink. The arrows at A point to the line of cardiopericardial adhesions. M, myocardium; P, pericardium. At B and C vessels are seen crossing directly between the pericardium and myocardium.

* Assistance by Drs. E. A. Fierro, Frank Fierro, Sidney Green, Melvin Rupp, Alden Raisbeck, Ralph E. Swope and L. P. Wershub is gratefully acknowledged.

Following the introduction of the talc powder a definite inflammatory reaction occurs and involves the pleura, the pericardium, the epicardium and the adjacent myocardium. One of the characteristic features of this reaction is the tremendous hyperemia which is produced within a few hours. The reaction persists for two or three weeks and gradually subsides. We feel that this hyperemia of the myocardium not only opens up the anastomotic channels between the coronaries which are already present, although not in use, but also stimulates the formation of new intercoronary channels. Thus the reaction would be responsible for the formation of new intracardiac as well as extracardiac collaterals.

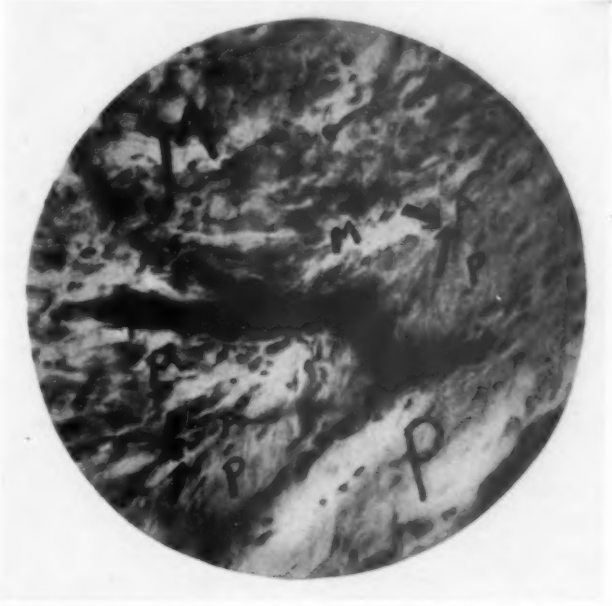


FIG. 2A. Photomicrograph (high power) of a section of a dog's heart following cardiopericardiopexy and ligation of a main coronary artery. The dog was sacrificed and the heart injected with India ink.

The arrows at A point to the line of cardiopericardial adhesions. M, myocardium; P, pericardium. Notice the large vessel filled with ink, crossing directly between the pericardium and myocardium.

Because of the inefficient lymphatic supply of the pericardium and the large size of the powder particle, very little if any of the powder is removed from the pericardial sac. Phagocytosis removes a small amount but the greater part of the powder remains indefinitely in the pericardial sac, fixed in the adherent tissues.

To determine the possibility of applying such a procedure to human beings, experiments were done on four groups of dogs. In the first group of 20 dogs the descending branch of the left coronary artery and vein were ligated and divided one centimeter below their junction with the circumflex

branch. In this group, which was used as a control, the mortality was 50 per cent. In the second group of 16 dogs, the same operation was performed but, in addition, talc powder was introduced into the pericardial sac at and around the site of ligation. In this group the mortality was 25 per cent. In the third group of 16 dogs, adhesive pericarditis was produced first by means of the talc and then, two or three weeks later, the same ligations and divisions were performed. In this group there were no deaths. These experiments demonstrated the ability of the pericardium to furnish a collateral circulation sufficient to overcome the ischemia produced by sudden, complete ligation of a main branch of the coronary artery, when adhesive pericarditis had been previously established.

In order to obtain further evidence upon the extent of collateral circulation from the pericardium, in a fourth group of eight dogs adhesive pericarditis was first produced as described above. After 14 to 21 days, the descending branch of the left coronary artery was ligated just below the circumflex branch. Two or three weeks after this operation the right coronary artery was ligated in its middle part. Following recovery from this operation the circumflex artery on the left was ligated at its origin. About 14 to 21 days later the right coronary artery was also ligated near the aorta. Thus there was no longer any direct supply of blood to the heart muscle, except through the collateral channels. Two dogs survived this extensive series of ligations; they could run and play with other dogs and were apparently well.

Robertson [40] reported a series of experiments in which by successive stages the coronary arteries were ligated up to their aortic origin and adhesive pericarditis was produced at the same time. Then, to determine the presence of a collateral circulation from any source other than the pericardium he removed the adherent pericardium, following which procedure none of the dogs survived.

In 1842 Chevers [10] demonstrated by autopsy material the presence of cardiac hypertrophy associated with adherent pericarditis only when additional pathologic changes existed which could account for the hypertrophy. Hosler and Williams [21] have shown from animal experiment and the analysis of 4,400 autopsy reports that adhesive pericarditis itself is usually silent and innocuous, does not play a significant rôle in the production of cardiac hypertrophy, and does not cause circulatory embarrassment unless it is extensive enough to cause cardiac angulation, torsion or compression.

It is necessary at this point to emphasize the difference between constrictive pericarditis and adhesive pericarditis. The two terms are often confused and considered to be identical, but they are, or may be, entirely different. The procedure which we advocate is the production of an adhesive pericarditis, and this is accomplished by our technic without producing constrictive pericarditis, as observation of the venous blood pressure at long intervals after operation has demonstrated.

As to the normal collateral coronary circulation, Wiggers,[48] in a com-

prehensive survey and a critical revaluation of available evidence, concludes that " the coronary anastomoses in normal hearts apparently have no functional value. This does not preclude the increase in calibre of the potential communications, or the development of a new system of vessels which can furnish adequate nourishment under pathological conditions. . . . As a result of the gradual narrowing of a coronary branch, the pressure within this branch decreases and the pressure gradients between intercoronary and extracoronary channels are favorable for a continuous flow towards the ischemic area during systole as well as diastole."

Augmentation of the coronary circulation by adhesive pericarditis may occur in any or all of three ways (figure 3): (1) by the formation of new

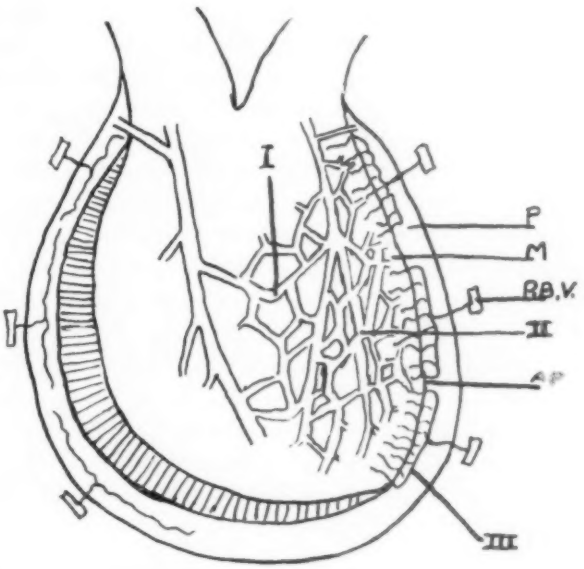


FIG. 3. This diagram illustrates the augmentation of the coronary circulation by adhesive pericarditis. (1) New channels form between the main coronary arteries. (2) Proliferation and dilatation of already existing intercoronary channels. (3) Formation of new extracardiac channels from the pericardium.

P, pericardium; M, myocardium; P.B.V., pericardial blood vessel; A.P., site of adherent pericardium to epicardium.

channels between the main coronaries, (2) by dilatation and proliferation of already existing intercoronary channels, or (3) by the formation of new extracardiac channels from the grafted pericardium.

OPERATIVE TECHNIC

In accordance with recent terminology we have called the production of adhesive pericarditis by operation, cardio-pericardiopexy. It is a simple operation and can be done in about 20 minutes. The procedure is as follows: an incision approximately three inches long is made over the left fifth costal

cartilage, the median end of the incision being at the costosternal junction. The incision is carried down to the costal cartilage. The perichondrium is incised and stripped from the cartilage anteriorly and posteriorly and about one and one-half inches of the cartilage is removed. The posterior perichondrium is incised for one and one-half inches, exposing the anterior mediastinum. Care is taken not to injure the internal mammary artery, which is now exposed. This artery and vein are retracted mesially. This approach is over the so-called free space and the pleura does not usually appear in the field. However, if it is present, it is gently retracted laterally, exposing the pericardium. The pericardium is picked up by hemostats and a one inch incision is made through an avascular area. A small rubber suction tube is inserted into the pericardial sac and any fluid present is removed. Five cubic centimeters of a 2 per cent solution of novocain are then dropped onto the epicardium to prevent fibrillation. This is allowed to remain in the pericardial sac for about four or five minutes and is then removed by suction. The heart is now palpated with one finger inserted into the pericardial sac. Any infarcts or scars are noted, as well as the presence or absence of adhesions of the pericardium to the epicardium. Approximately two drams of sterile, dry talc powder is now spread over the anterior surface and the inferior and left borders of the heart. The powder may be applied by a spatula or by an atomizer. The pericardial incision is now incompletely closed with No. 0 plain catgut. The posterior perichondrium is closed with fine catgut. The muscles of the chest wall, which were severed in the approach, are now approximated and the skin is closed. No drain is inserted.

The medical problems which arise in connection with the surgical treatment of coronary disease include the following: (1) the establishment of criteria for the selection of patients, (2) preoperative study and preparation, (3) postoperative management, and (4) the evaluation of results.

Selection of Cases

During the course of study of a new method such as cardio-pericardiopexy the selection of cases must be conservative and the criteria upon which selection is based must be made extremely rigorous.

At present we have limited ourselves to cases which can meet fully the following criteria. The first is a definite and clearly defined anginal syndrome, pain of characteristic nature and distribution, and particularly with a definite relationship to effort. This criterion is purely subjective but it is basic.

Of equal importance is objective evidence of coronary and myocardial disease in the form of positive physical, electrocardiographic and roentgen-ray findings.

Beyond these basic criteria we have added the following: the absence of improvement after fairly prolonged medical treatment and an extreme de-

gree of disability, corresponding at least to Class III of the Heart Association Classification, necessitating greatly limited physical activities. From the point of view of gaining a livelihood, most of our patients were in Class IV, unable to walk more than a few hundred feet without anginal pain and, therefore, completely crippled. Thus we have endeavored to take only cases that might have something to gain and practically nothing to lose.

A previous coronary occlusion is not considered a contraindication, rather the contrary as it constitutes definite proof of coronary disease. However, sufficient time must have elapsed to permit healing of the infarct, with no evidence of an active process still going on, and a further period of time is necessary to establish the fact that the patient still suffers from extreme limitation due to the myocardial condition. A fibrous scar following an infarct may not, of course, be influenced by any proffered new blood supply from pericardial adhesions or other sources, but we believe that bringing a fresh blood supply to other areas of the epicardium will be profitable.

Congestive heart failure is a contraindication to operation if there are any clinical evidences of passive congestion in the form of moisture at the lung bases, enlargement of the liver, or edema. Such findings increase the operative risk beyond a reasonable or safe point in our estimation. On the other hand, in some cases in which the dynamics of the circulation have been upset as shown by slowing of the circulation time and a rise in venous pressure, these manifestations have not been accepted as contraindications if the clinical findings were otherwise satisfactory. In two cases there were physical signs of congestive heart failure which had developed after previous coronary disease. Operation was performed after a preliminary period of treatment consisting of rest, digitalization and diuretic measures so that the patients came to operation after a period of complete freedom from the usual signs of passive congestion. Under these circumstances operation was well tolerated.

Preoperative Study

Our preliminary routine begins with a cardiological examination consisting of a detailed history, complete physical examination, routine electrocardiograms including at least two chest leads (CR–2 and CR–4) and roentgen-ray study (two-meter chest film and fluoroscopy). On the basis of this preliminary examination cases were selected and were then subjected to further study: determination of the circulation time, of the venous pressure by the direct method, and special electrocardiographic studies if ordinary records did not show positive findings.

It is of interest to note that in cases presenting the picture of pure anginal syndrome without apparent passive congestion on physical examination, we have found some slowing of the circulation time.

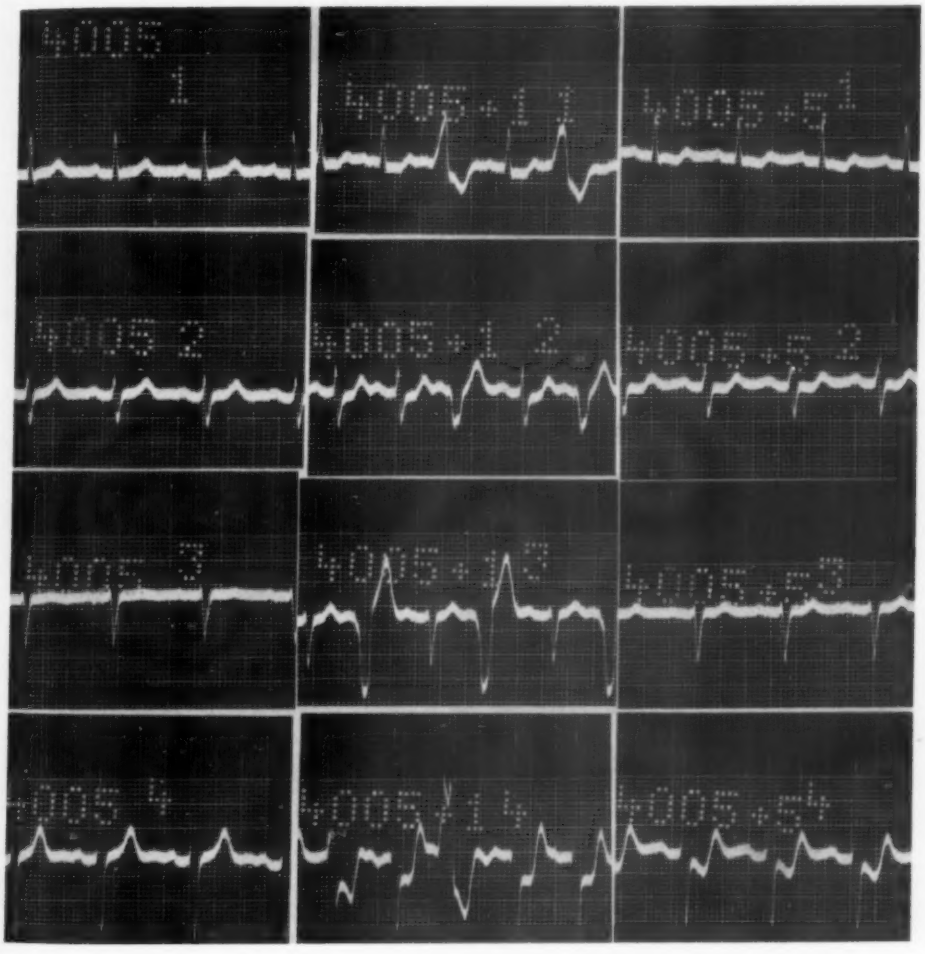
The determination of the venous blood pressure by the direct method showed some elevation in occasional cases. Our chief interest in the venous

pressure was to determine the preoperative levels for comparison in the future. Any obstruction to the return flow to the heart by reason of pericardial bands or adhesions should be detected relatively early by a rise in the venous pressure. It is our present belief that any difficulty in the future from pericardial bands or the like is not a real danger with this method. The adhesions which we seek to produce are limited to the area of application of the powder and do not tend to produce bands which have a constricting or tortional effect. So far our observations directly substantiate this belief, as the venous pressure after operation has in general remained normal or become somewhat lower than before, without any tendency to an abnormal rise in venous pressure during our period of observation, now extending to over three years.

Electrocardiograms taken at rest have given positive evidence of coronary arterial disease in a fair proportion of cases. In some of our patients we have been able to secure records from other observers taken during acute coronary occlusions in the past. If a record taken at rest lacks distinctive changes, two methods are open to permit more positive findings. One of these, exercise tests followed by serial electrocardiograms, has not been used as our patients were too ill to permit physical activity pushed to this degree. We have, therefore, used an anoxemia test which has given positive findings which fulfill our basic criteria when electrocardiograms at rest were not conclusive.

We have used a face mask which covers both the nose and the mouth, with a valve in the mask so that expired air is released at once. There is no dead space between the mouth and the valve so that the patient does not rebreathe any of his own CO_2. The mixture we use consists of 10 per cent oxygen and 90 per cent nitrogen. A control electrocardiogram is taken with a preliminary blood pressure reading. Then 10 per cent oxygen administration is begun, and every five minutes we take an electrocardiogram and blood pressure reading. The patient signals promptly if anginal pain develops or any other acute distress and, in that event, the test is stopped at once. If no adverse symptoms develop, the inhalation of 10 per cent oxygen is continued for 20 minutes. The patient is then given pure oxygen for three minutes and another final control electrocardiogram is recorded. In several of our cases the patient was unable to take 10 per cent oxygen for more than five or ten minutes without acute distress. In no cases have we observed the development of alarming symptoms or more than transient distress, but the occurrence of such symptoms is not acceptable as evidence of a positive test. We consider a positive test the occurrence of changes in the electrocardiogram of characteristic types: shifting of the S–T segment and variations in the amplitude and direction of the T-wave due to a subnormal state of oxygenation of the myocardium during the test. We have considered such changes as evidence of a subnormal coronary blood supply (figures 4, 5, 6, 7).

Our preoperative study is completed by tests which are intended to rule out the possibility of any active myocardial process due to a recent occlusion. In two of our earlier cases we believe that this feature of the study was not adequately covered, and it is highly important. The white blood count is

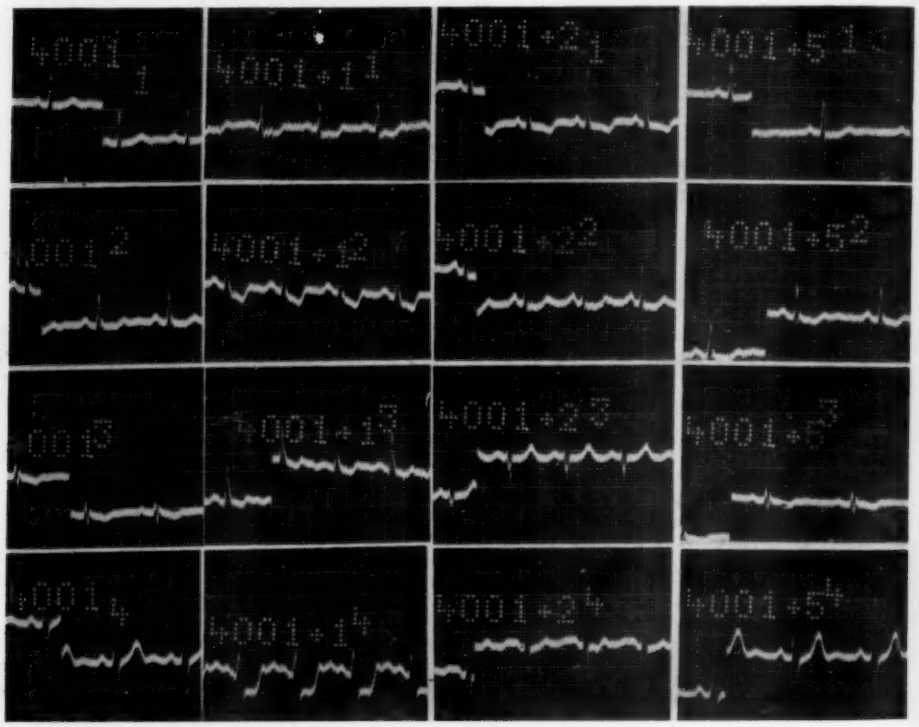


A B F

FIG. 4. Anoxemia test, case 8: A, control: B, after 5 minutes of 10 per cent O_2. Note lowering of the RS-T segments in Leads I, II and IV. F, after 3 minutes of pure O_2. This patient was not able to tolerate 10 per cent O_2 for more than 5 minutes.

helpful, but the red cell sedimentation rate is more sensitive and both should be done and should remain normal for at least two determinations about a week apart. In addition we have taken serial electrocardiograms at intervals of a few days to determine that the record is stabilized in its present form. These precautions tend to prevent, as far as may be possible, bringing a patient to operation with an infarct only partially healed.

Preoperative medication must vary according to the individual indications. In two of our patients who came to us in congestive heart failure we have used digitalis and the usual methods of treatment until all signs of passive congestion were cleared up. As a routine we give quinidine sulfate 0.20 gm. or gr. iii at intervals of four hours for several doses immediately preceding operation, the last dose timed within two hours of operation. This is intended to minimize the danger of the development of ectopic rhythms during operation. Preoperative sedation consisted of morphine



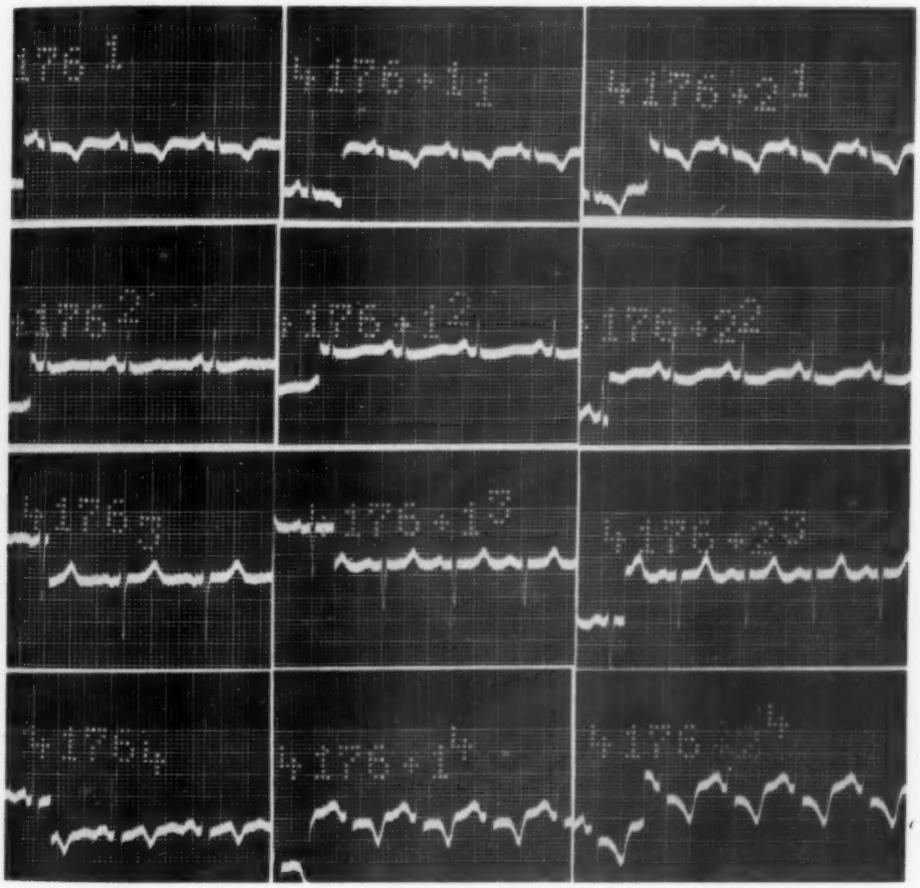
A B C F

FIG. 5. Anoxemia test, case 10: A, control: B, after 5 minutes of 10 per cent O_2. C, after 10 minutes of 10 per cent O_2. F, after 3 minutes of pure O_2. This patient was not able to tolerate 10 per cent O_2 for more than 10 minutes.

gr. $\frac{1}{6}$ to $\frac{1}{4}$, and atropine was given immediately before operation in doses of gr. $\frac{1}{100}$ and again immediately after operation.

The anesthesia used has been cyclopropane and oxygen, giving approximately 25 per cent cyclopropane and 75 per cent oxygen. If there were any signs of ectopic beats during operation, an extra dose of atropine gr. $\frac{1}{100}$ was given at once. Electrocardiograms were taken at short intervals during operation and only occasionally have we observed ventricular premature beats. Only rarely did two occur in succession and at no time have we had

evidence of ventricular tachycardia. As far as we can determine, this form of anesthesia is preferable for our purpose because of the large amount of oxygen which can be given and we do not feel that the anesthesia tends, under the circumstances in which we have used it, to favor the production of ectopic rhythms.



A B C

FIG. 6. Anoxemia test, case 7: A, control. B, after 5 minutes of 10 per cent O_2. C, after 10 minutes of 10 per cent O_2. In Lead IV the depression of the T-wave becomes more marked and the S–T segment is lowered.

POSTOPERATIVE COURSE

There is a febrile reaction with temperature reaching approximately 103° F. by the second or third day after operation. The elevation of temperature subsides gradually, in all lasting between 10 days and two weeks. In one case the temperature reached 104° F. and did not fall entirely to normal until three weeks had elapsed. No special cause could be found for

this prolongation of the febrile reaction, and the patient (Case 5) made a good recovery.

A pericardial friction rub is audible fairly promptly. We have not been insistent in attempting auscultation during the first day so as to avoid interfering with the operative wound. A friction rub has been heard definitely

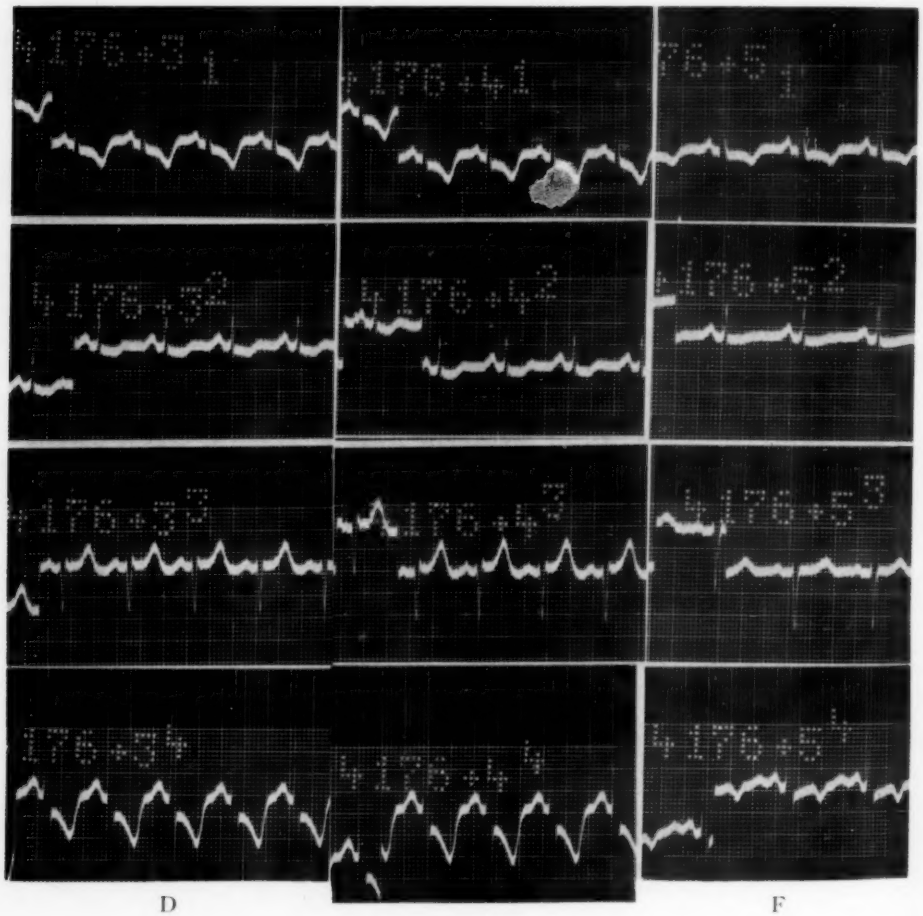


FIG. 7. Anoxemia test, case 7, continued: D, after 15 minutes of 10 per cent O_2. E, after 20 minutes of 10 per cent O_2. F, after 3 minutes of pure O_2.

on the second day and as the compresses are made smaller after the third day, it is heard over a wide area, practically the entire precordium, and persists upward of three weeks.

Within 24 to 36 hours of the operation we have regularly observed evidence of consolidation of the left lower lobe and in the first case we were alarmed by what appeared to be the development of postoperative pneumonia.

The physical findings are characterized by striking bronchial breathing and clear, high-pitched expiration, but with practically no râles or evidence of moisture in the alveoli. This change in the breath sounds is noticeable chiefly in the left axilla and below the angle of the left scapula. There is no cough or expectoration and the patient does not appear ill, as one might expect from the level of temperature and the bronchial breathing. Further observation in subsequent cases has made it clear that we are dealing with an inflammatory reaction, involving the contiguous tissues and lobe of the lung and characterized by evidence of consolidation but without exudate in the alveoli. For this we have used the term interstitial pneumonitis. The physical signs clear up within a week as a rule.

We have considered the possibility of compression of the lung by a pericardial exudate, but as far as we can determine by physical and roentgen-ray findings there is no demonstrable amount of fluid in the pericardial sac.

Inflammatory changes may involve the pleura and in two cases we have observed a small effusion on the left. This has been followed by adhesions in the left costophrenic angle, slightly limiting the movements of the diaphragm, such as we usually see after old attacks of pleurisy.

There is abundant roentgen-ray evidence of mediastinitis (figures 8A, 8B, 8C). Our first chest film is taken the day following operation and regularly shows enlargement of the mediastinal shadows which bulge out on each side during the first week of the postoperative period or a little longer. Clinical evidence of this was present in two cases in the form of mild dysphagia which lasted for about four days. Serial roentgen-ray films show regression of the mediastinal shadows, although they remain somewhat heavier than normal for several weeks after operation, clearing up slowly.

The electrocardiographic changes (figures 9 and 10), which are the subject of a separate communication, are characteristic of an acute pericardial reaction. There is concordant shifting of the S–T segment in the limb leads. In some cases the S–T segment in Lead III has shown a downward shift.

Postoperative medication has consisted of oxygen given as a routine during the first two days by double nasal catheter of the Bullowa type. There has been no respiratory distress and the color has remained normal, but it appeared reasonable to supply oxygen in order to spare the heart as much as possible. Sedatives have been used to control pain and in some cases to control cough. Moderate doses of morphine have sufficed and have not been needed beyond the second or third day. The need for continuing quinidine after operation has not been evident. As a rule ectopic beats or rhythms have not been observed. In our first case the appearance of bronchial breathing with the rise in temperature led us to use sulfapyridine (then available for investigational use under the name dagenan). Although we are not thoroughly convinced that chemotherapy is essential, it has

seemed wise to use it in order to limit any possible inflammatory complications. For this reason we have used moderate doses of sulfathiazole during the first three to five days until we are assured that the regression of the physical signs and the control of temperature are satisfactory.

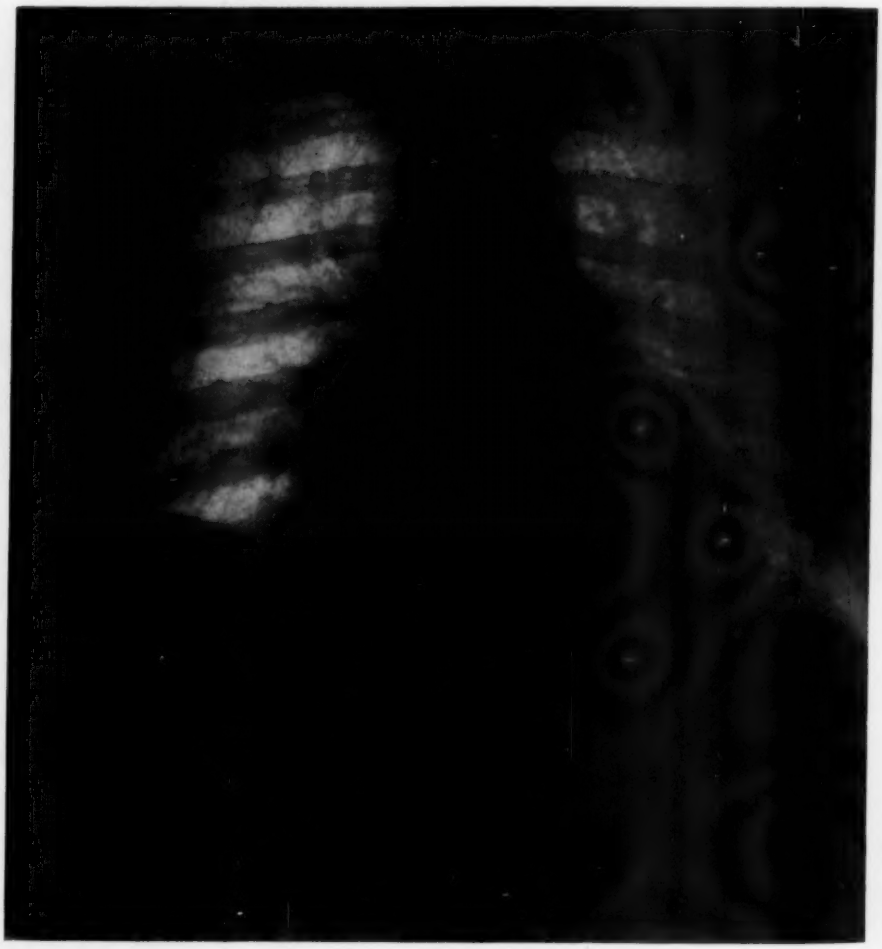
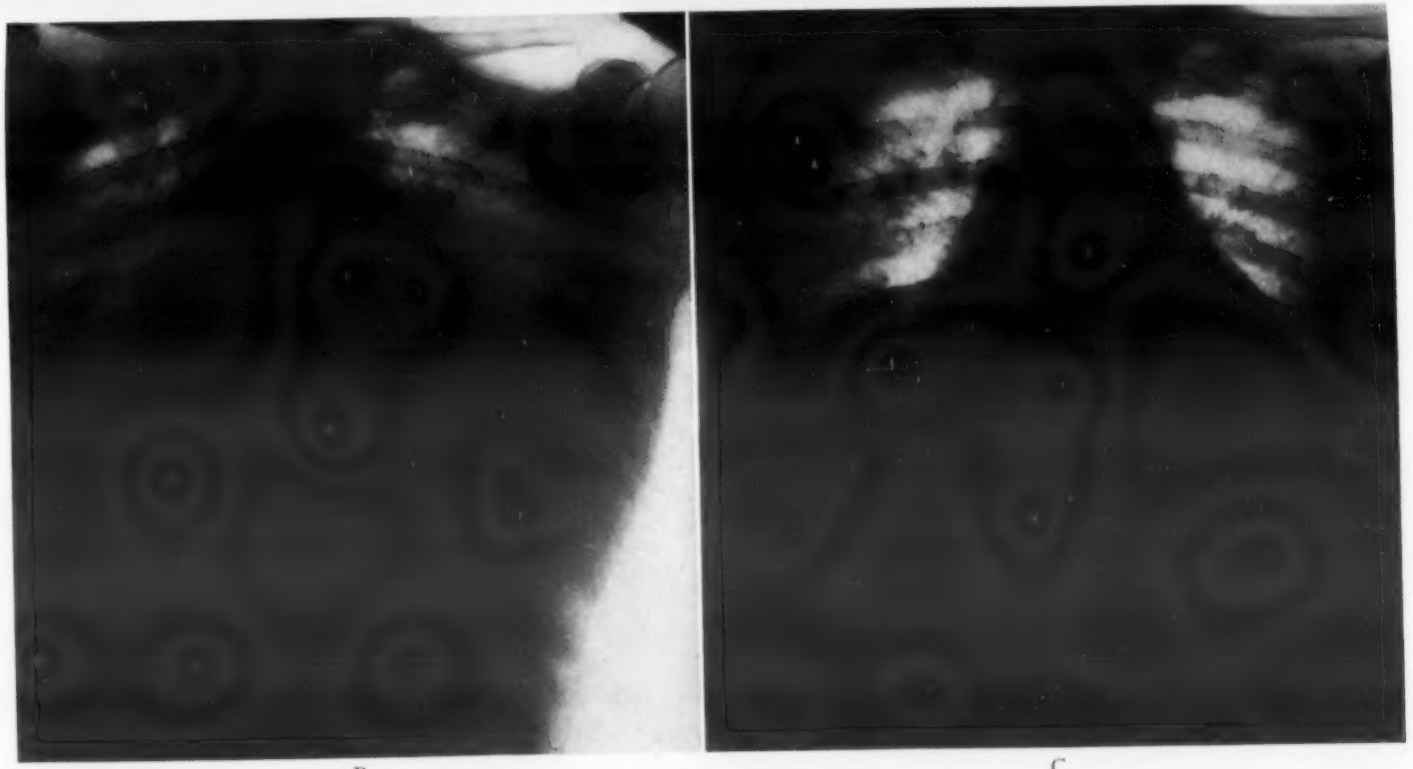


FIG. 8A. Roentgen-ray film of patient H. K. taken with a portable machine two days before operation. The portable machine was used so there could be a comparison with the pictures taken after operation.

Our clinical material has offered extra hazards because of the extreme degree of disability and recurrent anginal pain under the slightest provocation before operation. In spite of these undesirable factors in our clinical material the postoperative course has been fairly uneventful. The interstitial pneumonitis does not cause respiratory distress or cyanosis and cough requires only occasional medication. The patient does not manifest general



B C

FIG. 8B. Patient H. K. (same as figure 8A). This portable roentgen-ray was taken two days after operation. There is considerable increase in the width of the mediastinum. There is some increased density of both lung bases. Notice the inflammatory reaction spreading from the mediastinum out into the interlobar fissure on the right side.

FIG. 8C. The same as figure 8B, but taken nine days after operation. The mediastinum has decreased in size. The inflammatory reaction around the mediastinum is not as pronounced and the physical signs at this time were normal.

FIG. 9. FIG. 10.

FIG. 9. Case 1: A, electrocardiogram before operation. B, four days after operation, showing elevation of the RS–T segments due to the pericardial reaction.

FIG. 10. Case 4: A, electrocardiogram before operation. B, seven days after operation showing definite evidence of the pericardial reaction. Elevation of the RS–T segments in Leads I and II.

illness or depression such as we would expect in pneumonia and there is a marked contrast between the objective and the subjective findings.

There is some distress in moving the left arm or shoulder which is due to the attachment of the pectoral muscles in the neighborhood of the operative wound. This has been controlled by mild sedatives but may persist for several weeks after operation. Painful left shoulder may develop as a late manifestation in coronary disease and is a familiar clinical entity, particularly in cases that have formerly suffered occlusion and infarction. This may be a complicating factor as far as left shoulder pain is concerned in our patients, but we have the distinct impression that local conditions affecting the pectoral and other muscles of the shoulder girdle adequately explain the symptoms. Distress from this source has not hampered recovery and clears up within a few weeks.

Evaluation of Results

In the selection of cases we have been guided by the principle that operation is justified if the patient has nothing to lose and possibly something to gain. Thus our group of cases represents cardiac derelicts with advanced coronary disease and under ordinary circumstances a hopeless prognosis. We have been surprised and encouraged to note that they tolerated operation so well and that the postoperative course went on as smoothly as it has done in most of our series.

Three patients died a short time after operation, one within a few hours and the other two on the second day. A fourth patient died three weeks after operation. In the patient who died within a few hours we were dealing with recurrent anginal pain at rest which had kept the patient bedridden for some time. We do not believe that we were sufficiently alert to the fact that an active process was present and subsequently in other patients we were able to rule this possibility out by additional serial determinations of the sedimentation rate and serial electrocardiograms.

In one patient dying on the second day an autopsy could not be secured, but we suspected either a fresh coronary accident or a pulmonary embolus.

Our total series now numbers 13 * and of the nine remaining patients none has failed to secure some relief, which has been striking in several cases, permitting a return to normal exercise capacity. The results are of greater interest in proportion to the length of time that has elapsed since operation. Our first case now dates back over three years and the improvement is marked (estimated by the patient as 75 per cent) and in our second case, dating back nearly two and a half years, the patient shows marked improvement and has a normal exercise tolerance.

The clinical notes herewith give the details of each case as far as our period of observation extends.

* Since this report was received three additional patients have been operated upon with excellent results in all up to the present time.

Case Reports

Case 1. O. S., business man, aged 39, was first seen in September 1936, during the acute phase of a coronary occlusion with typical electrocardiographic evidence of anterior wall infarct. Pain was so severe that it could not be controlled by morphine and required para-vertebral block October 1, 1936. Thereafter he was crippled by anginal pain and when seen again in November 1938 was stopped on an average of three times within a short block by acute chest distress, which also came on after excitement. Electrocardiogram on November 22, 1938 showed slight depression of T_1 and R-wave lacking in Lead CR–2. Cardio-pericardiopexy was performed November 25, 1938. There was electrocardiographic evidence of the usual pericardial reaction and sharper depression of T_1. The venous pressure 18 months after operation was 88 mm. H_2O, and two years after operation was 70 mm. H_2O. The clinical course since operation has been as follows. Following operation the patient increased his activities without precordial distress until February 20, 1939 when, after shoveling snow, he had severe chest pain. He gradually became active again, and in June 1939 there was severe chest pain following overexertion playing ball. At present he reports chest pain only when he lifts anything heavy or overexerts himself. He can walk more than a mile without distress and if he does not hurry he can be active all day without symptoms. Chest distress tends to come on more easily after a meal. He feels that he is greatly improved and estimates the improvement as 75 per cent. Compared to his state of complete disability between 1936 and 1938 we estimate this result as marked improvement, now more than three years following operation.

Case 2. B. S., a business man, aged 47, was first seen December 1938. In April 1938 a coronary occlusion had occurred for which the patient was admitted to the Lenox Hill Hospital. In December 1938 the electrocardiogram showed an atypical right bundle branch block. Anginal pain was so severe and frequent that he carried on his business as a wholesale paper dealer in a wheelchair. Before operation anginal pain occurred after climbing 44 steps. Cardio-pericardiopexy was performed January 11, 1939. In February 1939 he was able to walk five or six blocks at a time without distress and resumed normal activity gradually. In July 1939 he was doing a full day's work, calling on customers from nine to six daily, on his feet steadily, occasionally climbing stairs, but avoiding heavy lifting. The electrocardiogram showed no additional change. In March 1941 another coronary occlusion occurred (posterior wall). In May 1941 the electrocardiogram showed additional changes due to a posterior wall lesion. Recovery from this episode was quite satisfactory and in July 1941 the patient was normally active, without chest distress. The venous blood pressure has varied between 80 and 90 mm. H_2O after operation up to the present time. The degree of improvement here is marked. This patient has shown rapid recovery from an additional coronary occlusion since operation with return to normal exercise tolerance.

Case 3. S. E., valet, aged 58 years. At the age of 56 he reported pressure and pain on effort over the lower third of the sternum and at the age of 57 the onset of effort dyspnea. Passive congestion developed rapidly and in February 1939 there was massive edema of the legs. Digitalization and medical care before admission to the hospital did not control the congestive failure. He was admitted to the Flower-Fifth Avenue Hospital on February 16, 1939. The electrocardiogram showed small diphasic T_1 and in Lead CR–4 a small slurred group of initial deflections with a relatively deep and broad Q-wave. Congestive failure receded under digitalization and diuretic therapy, and on March 15, 1939 cardio-pericardiopexy was performed. The postoperative course was uneventful, and from April to December 1939 the patient was free of symptoms and back at work involving long hours on his feet daily. In January 1940 effort dyspnea recurred with general fatigue and since then the patient has required 0.10 gm. digitalis daily for comfort. This case is an example of coronary

disease followed by congestive failure which did not respond to medical treatment until after operation. The degree of improvement may be considered moderate as the patient still needs some digitalis to carry on in comfort, but he follows a full program of work.

Case 4. H. E. O., salesman, aged 50. On August 17, 1938, a coronary occlusion occurred with anterior wall infarct and an electrocardiogram submitted, taken September 19, 1938, showed some depression of T_1 and T_2. In April, 1939 there was frequent chest pain occurring at rest and aggravated by exercise. Cardio-pericardiopexy was performed May 3, 1939. The postoperative course was complicated by wound infection by a gas forming bacillus later identified as *Bacillus welchii*. Local healing was slow but the general condition remained satisfactory. In May 1941 the patient reported complete absence of chest pain. At his best before operation he was able to walk four or five blocks and, therefore, improvement may be considered marked, with complete relief from angina.

Case 5. G. A., housewife, aged 36. This patient complained of frequent chest pains and fainting attacks. The electrocardiogram at rest showed a low T_2, and under anoxemia there was a further flattening of the T-wave in this lead. The clinical picture was not typical and after a first admission in February 1939 operation was withheld. Symptoms, however, increased and after readmission in July 1939 cardio-pericardiopexy was decided upon and performed July 13, 1939. The postoperative course was uneventful, except for the fact that fever lasted for a longer period than usual, up to three weeks. Upon discharge on August 4, 1939, there was marked subjective improvement, and this has been maintained to date. In July 1941, the patient had to go back to business on account of the illness of her husband. This involves commuting from New Jersey daily, leaving home at 7:30 a.m. with a 15 minute walk on arriving in the city and a similar one to get home at night. Chest distress occurs after marked excitement or if she hurries, but she is able to carry on. There is a great deal of fatigue toward the end of each week, but she estimates her improvement as 70 to 80 per cent, now permitting gainful occupation under severe strain, quite impossible before operation. Therefore the degree of improvement may be considered marked.

Case 6. J. D., machinist, aged 59 years. The chief complaint was substernal, burning pain associated with effort. The electrocardiogram August 3, 1939 showed depression of T_2 and T_3. During the anoxemia test the RT segment in Lead I was lowered, T_1 became diphasic, and with further anoxemia the foot-point of T_3 became elevated. Cardio-pericardiopexy was performed August 7, 1939. Venous pressure before operation was 130 and after operation on August 9, 210 mm. H_2O. Shortly after operation dyspnea developed and death occurred on August 9, 1939. Autopsy showed a recent infarct in the posterior wall of the left ventricle extending from a point 2 cm. above the apex to the base of the ventricle. Death occurred as a result of fresh coronary occlusion with acute dilatation of the left heart and multiple pulmonary infarcts resulting from mural thrombosis of the pulmonary artery.

Case 7. J. B., bartender, aged 52. For the preceding three or four years the patient had complained of pain in the left chest and left arm, progressively worse, associated with hypertension. He had been overweight, reaching 240 pounds, but had dieted down to 200 pounds when first seen in August 1939. On August 18, 1939 the electrocardiogram showed a small diphasic T_1 and in the course of the anoxemia test there were additional changes: sagging of the RT segment in Lead II and later marked depression of T_1 which returned toward normal after inhalation of pure oxygen. Cardio-pericardiopexy was performed August 18, 1939. Venous pressure before operation was 190 mm. H_2O. Three days after operation it was 260 and 12 days after it was 180 mm. H_2O. Postoperative course was uneventful. Since operation the hypertension has persisted, but there has been complete relief of the anginal pain. He can now walk up to a mile at a time without distress and is back at work.

Case 8. M. W., business executive, aged 59 years. He had been well up to the age of 56. In July 1936, after swimming, he had prolonged and severe chest pain. After that he was able to walk only about two or three blocks and occasionally four blocks, but was severely limited by anginal distress. The electrocardiogram at rest did not show distinctive changes, but under anoxemia there was depression of the RT segment in Leads I and IV with frequent ventricular premature contractions. T_4 became quite diphasic and the patient's distress was so acute that 10 per cent oxygen could not be continued for more than five minutes. Cardio-pericardiopexy was performed August 21, 1939. The venous pressure after operation on August 23 was 180, on August 30, 120 and on September 12, 150 mm. H_2O. Severe attacks of chest pain lasting 15 to 20 minutes occurred at various intervals before operation, and since operation he has had no attacks. He is now able to walk up to 15 blocks at a time without distress, although slight chest distress does occur after climbing two flights of stairs. He estimates his improvement as 90 per cent and is now back at work.

Case 9. I. P., ticket seller, aged 54, complained of substernal and precordial pain radiating to the left shoulder and arm during the preceding two years. On August 17, 1939, walking slowly up 10 steps caused mild substernal pain radiating to the left arm. The electrocardiogram at rest showed depression of the T-wave in all the limb leads and diphasic T_4. Under anoxemia this depression became more marked with lowering of the foot-point of the T-wave particularly in Leads I and II. Cardio-pericardiopexy was performed October 18, 1939. The venous pressure before operation on October 17 was 170 mm. H_2O and was higher after operation, reaching 200 on October 18, 1939. On October 19, the general condition appeared satisfactory with no difficulty in respiration but later the same day the venous pressure was found elevated (230 mm. H_2O). On October 20 the patient complained of pain and restlessness. The venous pressure was found to be 240 mm. H_2O and death occurred on this day, apparently of acute congestive heart failure. Autopsy was not permitted.

Case 10. O. E. W., physician, aged 50 years. In November 1934, at the age of 46, he first noted chest distress while walking, which at first was only occasional and mild, after unusual exertion. This became progressively worse so that in July 1939, on an empty stomach, he could walk slowly about 150 feet but faster walking stopped him within this distance. At rest the electrocardiogram did not show distinctive changes, but after exercise there was a definite lowering of the foot-point of T_1 and T_2. On November 7, 1939 one flight of stairs produced severe anginal pain. Cardio-pericardiopexy was performed November 8, 1939. Before operation the venous pressure varied between 155 and 160 mm. H_2O. After operation on November 9 it reached 165 and once after getting up on November 14, 230 mm. H_2O. After that the venous pressure was between 95 and 110 mm. H_2O. Upon discharge from the hospital he was able to walk up two flights of stairs with only slight distress. Since then he has resumed practice limited to eye, ear, nose and throat work, with occasional tonsillectomies and minor nasal operations. Walking causes chest distress but he has resumed practice which he was unable to carry on before operation. We believe there has been a definite improvement but of moderate degree.

Case 11. J. B., mechanic, aged 64. The patient complained of chest pain during the preceding three years with much limitation of activity, Class III. The electrocardiogram showed evidence of atypical intraventricular conduction defect. Cardio-pericardiopexy was performed December 8, 1939. The postoperative course at first did not show unusual features, but tachycardia, weakness and air hunger developed on December 24, 1939, with collapse, and the patient died on December 30, 1939. Postmortem examination showed a fresh infarct in the posterior wall of the left ventricle. There was a complete obliteration of the pericardial sac with the pericardium adherent to the myocardium. The pericardial vessels were congested and engorged. Injection of one of the pericardial vessels with India ink demonstrated the passage of the ink into the myocardial vessels.

Case 12. W. H. S., clerk, aged 48. The patient was completely crippled by anginal pain recurring at rest while in bed. The electrocardiogram at rest showed practically flat T-waves in the limb leads. He could tolerate the anoxemia test for only five minutes and then showed some lowering of the RT segment in Lead I. The venous pressure was elevated before operation, on January 26 it was 340 and on January 28, 1940, 260 mm. H_2O. Cardio-pericardiopexy was performed January 30, 1940. Death, which occurred about half an hour after operation, appeared to be due to ventricular fibrillation. Autopsy showed marked calcification of both main coronaries with complete occlusion of both these arteries. There were several old infarcts and one very recent infarct in the left ventricular wall.

Case 13. H. K., furrier, aged 47 years. At the age of 44 pain in the left chest occurred. On January 16, 1939, the symptoms of coronary occlusion were so severe as to require hospitalization for six weeks. Thereafter his activities were limited by chest pain (Class II). December 8, 1940, a second coronary occlusion occurred and he was in the hospital about 7 weeks. Following this attack pain on effort was more severe, causing greater limitation (Class III). The electrocardiogram showed a low T_1 and diphasic T-wave in Lead CR–4, without marked changes during anoxemia. Cardio-pericardiopexy was performed March 7, 1941. The venous pressure on March 5 was 120 and on March 6, 115 mm. H_2O. After operation the venous pressure recorded on March 9 was 90, on March 17, 120, and on March 22, 80 mm. H_2O. In May 1941, T_1 was sharply inverted and T_2 small and diphasic, but the exercise tolerance showed marked improvement. He was able to walk up to a mile without chest distress. The period since operation to date has only been four months, but so far the degree of improvement is marked.

If the improvement is graded as follows, + slight, ++ moderate, and +++ to ++++ marked, these results from the clinical point of view may be summarized as follows:

Case	Time Elapsed Since Operation	Clinical Result
1	2 yrs. 8 mos.	+++
2	2 yrs. 6 mos.	++++
3	2 yrs. 4 mos.	++
4	2 yrs. 2 mos.	++++
5	2 yrs.	+++
6	—	died
7	1 yr. 11 mos.	+++
8	1 yr. 11 mos.	+++
9	—	died
10	1 yr. 8 mos.	++
11	—	died
12	—	died
13	4 mos.	++++

In all, four cases have died, two show moderate improvement, and seven show marked improvement.

Summary

Cardio-pericardiopexy, or the production of adhesive pericarditis, can be accomplished regularly by the introduction of sterile talc into the pericardial sac, and the technic of the operation has been described.

Animal experimentation has demonstrated the ability of the pericardium to furnish a collateral circulation to the myocardium, sufficient to overcome

the ischemia produced by sudden complete ligation of a main branch of the coronary artery when adhesive pericarditis had been previously established.

Cardio-pericardiopexy produces a collateral myocardial circulation by any or all of the following ways: (1) formation of new channels between the main coronary arteries; (2) dilatation and proliferation of already existing intercoronary channels, and (3) formation of new extracardiac channels from the newly adherent pericardium.

It is entirely possible that the beneficial effects of this operation may be due as much to the formation of intracardiac collaterals resulting from the myocardial reaction as to the formation of new extracardiac collaterals from the adherent pericardium. Although the reaction subsides and the stimulation of the operation ceases, the original impetus may accelerate the process of spontaneous collateral formation to a rate equal to or greater than the occlusive process.

The criteria which we have used in selecting these patients for operation have been enumerated. It is hoped that additional experience will enable us to extend the present indications to include a larger group of patients.

The preoperative study and preparation of the patients for operation, as well as the postoperative management, have been reviewed.

The evaluation of our results is gratifying. A group of cardiac derelicts who were completely incapacitated have been relieved of their anginal pain and have returned to their former occupations. The relief from angina is complete in some and partial in others. No patient in our series has failed to show symptomatic relief and a definite increase in his exercise tolerance.

Follow-up examinations of all patients, which include exercise tolerance tests, blood pressure, direct venous pressure, fluoroscopy, roentgen-ray and electrocardiographic examinations, fail to show any evidence of cardiac compression or cardiac hypertrophy due to adhesive pericarditis.

The simplicity of the operation and the benefits that have accrued to the patients would seem to warrant further employment of this procedure. It has been performed at our suggestion by one other surgeon with good results.* We feel, therefore, that we are dealing with a method which should give good results in any competent hands.

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ELECTROSTETHOGRAPHY. 1. CATHODE RAY VISUALIZATION OF LUNG CHEST SOUNDS*

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The analysis of sounds and vibrations requires visual methods for detail study. The value of visual methods has been demonstrated in many technical fields. Percussion, palpation and auscultation, being tactile and aural methods, are handicapped both in the classroom and the clinic because of the lack of convenient and reliable methods for demonstrating the vibrations. Our teaching of physical diagnosis contains too many words which fail in the attempt to describe sounds heard in the chest. These words are apt to lack descriptive value in themselves and our further attempts at describing the sounds we hear too often demonstrate how far apart some of us are in our understanding of the more delicate meanings of words. This language difficulty is not only a problem in physical diagnosis; it is interesting that the same turbidity of speech occurs in the descriptions used in echo navigation where we find echoes referred to as "sighing," "grating," and "booming," according to the type of terrain reflecting the sound.[1] In contrast, when such vibrations are converted into wave forms by a suitable recorder the differences in the vibrations become visually apparent and the results are accurately describable in terms of amplitude, frequency, harmonic and nonharmonic content, etc. Our attempts to demonstrate visual wave forms to the uninitiated have convinced us that it is not at all difficult to shift our usual method of thinking about vibrations to a visual wave form picture. By listening to chest sounds and seeing their wave forms it has been our experience that one becomes aware of finer distinctions in sounds and at the same time one realizes the superiority of visual analysis.

Various visual methods of sound recording have been used in physical diagnosis, including the early work with manometric flames and revolving mirrors; later the use of tambours and mirrors; and more recently stethoscopic pickups in conjunction with electric amplifiers and mirror-type tension galvanometers. Major's text on physical diagnosis records a few chest sounds using a cathode ray tube circuit.[2] These methods have in general been technically difficult to operate or the apparatus has had frequency characteristics which restricted the value of the results obtained. Some of the component parts in the methods used in the past are still subjects of controversy; for example the filtering effect of rubber tubing, the lack of line-

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arity in the frequency response of diaphragms, the shapes of stethoscope bells and the air pockets enclosed. The inertia and restoring torques of galvanometers have affected the frequency characteristics of some of the equipment used. The range of uniform frequency response is surprisingly limited in some of the tension wire type of galvanometers. In spite of these handicaps useful and serviceable apparatus has been developed for the recording of heart tones although some of these devices filter out certain vibrations which might well be of clinical interest. From our experience the recent instrument developed by Kountz and associates [3] and the one by Boone [4] are advances in meeting the problem of fidelity of recording.

Many terms have been used to name the instruments designed for the recording of heart tones. Greater uniformity would be distinctly desirable from the standpoint of indexing. The term "stethograph" could well be used as the generic classification for apparatus which records sound waves and vibrations graphically. Our suggestion is that "electrostethograph" be retained as a subdivision, which should include stethographs in which vibrations are picked up by direct contact without involving tubing or air compartments, and in which the amplification and recording are purely by electrical means. The particular characteristics available in electron amplifiers and the cathode ray types of tubes are sufficiently distinctive to warrant this subdivision. The term "electrostethograph" was first proposed by Bierring, Bone and Lockhart [5] but in the later development of their apparatus by Lockhart the term "stethograph" was used.[6]

Method

Recent developments in electronics permit the easy design of visual recording apparatus which will accurately record vibrations over wide frequency ranges. The uniform response of crystal type microphones permits the use of a compact microphone with an ample voltage output. We used the Shure 66 D type which has a contact face diameter of 0.75 inch and a mechanical connection between the contact button and the crystal making it sensitive to all contact vibrations but relatively insensitive to air-borne vibrations. This avoids the filtering problems due to rubber tubing, diaphragms, or stethoscope bell shapes. The frequency response is linear up to 1500 cycles per second but is reduced by 10 db at 2000 and 25 db at 8000 cycles. This frequency range is more than adequate for all sounds encountered in chest work.

The amplifier was resistance-coupled, single-ended and with a time constant of one second. With properly designed circuits and using a 3 inch cathode ray tube it was possible to assemble the complete apparatus, except for the cameras, in a small leatherette case with a total weight of less than 15 pounds. (Figure 1.) In part of the work a filter condenser was inserted into the input circuit changing the time constant to about 0.2 second.

The cathode ray tube circuit was conventional, the short persistence type of tube being used because of the greater photogenic power of the blue end of the spectrum.[7] A sweep circuit was included using a type 885 tube, and provisions were made for locking the sweep to the wave forms being stud-

FIG. 1. Electrostethograph. The lid has been removed showing the various controls. The single exposure camera or the moving film camera is fastened by a bracket in front of the cathode ray tube.

ied. A bracket was mounted at the end of the case to hold the cameras. For single exposures (to be described later) a commercial 35 mm. camera with an f 3.5 lens was used. For continuous film exposures the escapement mechanism was removed from an 8 mm. movie camera, alternate teeth were

removed from the driving drum to permit the use of 16 mm. film, and the lens was refocused. The governor was then readjusted. This gave a compact continuous film camera.

Although the equipment was constructed for the study of chest sounds of various types our particular interest here was in the question of transmission of lung sounds to the chest wall. A source of vibration was necessary and several were tried. We used ordinary percussion as a source of vibration, as well as several mechanical vibrators in which the amplitude and frequency were adjustable. Since this method involved a vibrator which varied in position on the chest wall and a microphone pickup, which was moved about the chest, relationships were complex. Transmission along the ribs was troublesome. It would have been an advantage, we think, if the percussor and the microphone were made into a single unit. The percussion blow would of course give a large deflection on the cathode ray screen but following this one would get the vibration response of the chest to the blow. Attempts to locate the percussing instrument at some fixed point on the chest wall which would be suitable for a study of the entire chest were not very successful.

We next tried transmitting the vibrations to the chest by means of a Jensen 8 inch speaker fitted with a funnel-shaped enclosure covering the diaphragm. Large heavy tubing was connected from the spout to the mouth of the subject. The speaker was operated at various frequencies and energy levels by a sine wave generator. The microphone was placed in contact with the chest wall and the transmitted wave forms studied. Variations in transmission and harmonic components were noted and the normal relations, to be described later, could be observed, but this method required too much cooperation on the part of the subject to be of practical clinical use.

The " loudspeaker " method did show some potentialities, however, which might make it of value in studying certain aspects of lung physiology. Since the source sound was produced electrically it was possible to apply this frequency from the sine wave generator to the horizontal plates on the cathode ray tube in place of the sweep circuit. Keeping the amplified vibrations picked up from the chest wall still connected to the vertical plates, the resultant figure seen on the tube is made up of the deflections laterally due to the source frequency while the vertical deflections are the source frequency as picked up after being transmitted through the chest. If the transmitted wave suffered no changes other than amplitude the resultant wave form would be a circle or an ellipse. The formation of harmonics would appear as waves superposed on the closed curve. Changes in the phase between the source and the picked-up wave appear as sloping of the elliptical patterns to right or left. These figures are known as Lissajous figures and are widely used in the study of distortions in amplifiers, frequency measure-

ments, etc.* This method showed a marked increase in harmonic content in the wave forms occurring at the end of expiration as well as various phase shifts during respiration depending in part upon the tenseness of the throat and shoulder muscles, and the way the subject controlled the mouth and muscles of the pharynx. The effect of frequency on wave form could also be observed.

The method finally adopted was to have the subject phonate at his natural frequency. In ordinary speech electrostethograms show that if a microphone is placed in contact on the neck at the side of the larynx the wave form observed comprises a " fundamental " frequency which is relatively constant with various overtones superposed on this fundamental. Fahr in his discussion of Martini and Mueller's studies on percussion and auscultation uses the term " fundamental " for the relatively constant frequency and " formative " for the overtone portions.[7] If the subject says " A-h-h-h-hH " or " Ni-i-i-i-Ne " the pattern, except for starting and stopping, is relatively constant, and the lowest frequency varies from about 90 to 200 cycles per second. Under these circumstances the wave form obtained would seem to approximate the carrier wave form as pointed out by Dudley in his discussion of the development of the Voder, an instrument for the artificial synthesis of speech.[9] Such a natural frequency can be maintained easily by most individuals, and the wave forms picked up by the microphone at various parts of the chest wall are reproducible. In the same individual moderate variations in this fundamental or carrier wave frequency do not markedly change the wave shapes obtained. At high frequencies there is some simplification of the wave forms obtained and it is characteristic that chest wave forms are simpler in harmonic content in women than in men. If the subject phonates at a moderate intensity the variability due to variations in respiratory volume and to approaching expiration are not observed, in contrast to the loudspeaker method.

During the observations the subject should be in a comfortable and relaxed position. Tensing of the thoracic muscles can increase harmonic content and the results are not easily reproducible. Ambulatory patients sit on a short stool, somewhat roundshouldered in posture with the arms resting comfortably at the side. These details are the same as those used in percussion of the chest.

* Due to space limitation it is impossible to give any discussion of harmonic wave analysis. Numerous machines have been devised for analyzing harmonic wave forms and the mathematics of the more complex wave motions is highly technical. However, much useful information can be obtained from wave form studies without a knowledge of the mathematics of wave motion. Sound Waves, Their Shapes and Speeds, by D. C. Miller (Macmillan, 1937) gives an excellent and easily readable description of sound waves. The Radio Corporation of America Technical Bulletin TS-2 illustrates some of the Lissajous figures used in frequency determinations. The Cathode-Ray Tube at Work by John F. Rider, 1935, Chapter V, gives an elementary description of Lissajous figures and phase relationships. Engineering Mathematics, C. P. Steinmetz, McGraw-Hill Book Company, 1917, Chapter VI shows in a number of figures the effects of varying the amplitude of different harmonic components.

Having the subject phonate, the sweep circuit frequency is adjusted until the wave forms stand still. This occurs whenever the chest wave frequency is some multiple of the sweep frequency. Using the 3 inch cathode ray tube the sweep is adjusted so that four or five complete cycles appear on the screen. This spreads a cycle out to about 2 cm. and is sufficient to make frequencies up to 1000 cycles per second easily visible. If higher frequencies are to be studied the sweep can be accelerated until only one cycle appears on the screen, giving a spread of about 3 inches. The amplitude of the chest wave forms is then adjusted by varying the gain control of the amplifier. Having the subject phonate each time, the microphone is moved to a new position while the examiner observes the wave form. Occasionally the subject will change his frequency sufficiently so that the waves do not remain stationary but move to right or left across the fluorescent screen. The apparatus is provided with a synchronization control or locking device which can be adjusted to keep the sweep and chest waves in synchronization over a considerable range. With some individuals no locking is necessary. If movement of the wave occurs then: (1) the sweep frequency can be readjusted, (2) locking can be used, or (3) the subject can readjust his frequency a little. In the last situation on a few occasions we have connected an earphone to our sine wave generator and adjusting this to the subject's fundamental frequency, we have permitted him to hear this sound. He will then return to pitch. Before starting a series of observations we try to determine with a few trials the frequency the subject can maintain most easily. By engaging him in conversation, this fundamental frequency becomes apparent and if he tries to say " Ni-i-i-i-Ne " at a different frequency, we encourage him to say it more naturally.

Since by the phonation method the chest sounds are harmonic, i.e., uniformly periodic in character, it is possible to have them appear at the same position on the screen by the electrical means described. The appearance to the observer is that of a train of wave forms standing still during the phonation. Aside from permitting convenient visual observation it is also possible to photograph them with a snapshot camera. Using a standard 35 mm. camera 36 exposures may be made on a single roll of film. The single exposure method results in marked film economy as compared to a method omitting the sweep and using continuous moving film. For example, to spread the wave forms out to one inch per cycle would require 90 inches film travel per second for a frequency of 90 cycles per second.

When studying phonation sounds the heartbeats of course appear on the fluorescent screen and are quite marked on the left side in front. Since the first and second heart tones are considerably lower in frequency the effect of the heart beat is to move the base line of the chest sound up and down. Since there are many chest waves to one heart beat, this movement does not interfere with adequate perception of the chest wave. The heart beats do not appear on the photograph. With excessively loud murmurs probably a

study of chest sounds in the region of the heart would require further apparatus considerations. So far we have not experienced this difficulty. When photographing the chest sounds the operator observes the wave form on the fluorescent screen and releases the shutter during the midportion of the phonation. We prefer a between-the-lens shutter on the camera because focal plane shutters, especially those that move in the same axis as the sweep, may miss the wave entirely.

A holder for the microphone is of great value and figure 2 illustrates a suitable type. This suspends the microphone in the middle of a band of

FIG. 2. Holder for microphone, and side view of electrostethograph.

rubber and thus separates the movements of the operator from the subject. At the same time the holder permits the microphone to move a little with the movements of the subject without slipping along the skin. The holder is placed usually so that it is parallel with the ribs and pressed firmly enough so that the end pieces are against the subject's chest. Static microphone pressure is not critical.

Excessive dryness of the throat will occasionally simplify the wave forms obtained. Excessive mucus in the pharynx as from postnasal catarrh may

at times interfere with reproducible results or produce rhonchi. Clearing the throat and coughing will eliminate these. Since the amplitude of the wave forms is of interest it is advisable to place the microphone on alternate sides of the chest instead of making a series of observations on one side before studying the other side. This is particularly advisable when studying patients who are weak or who tire easily. Errors from this source have been eliminated in a more recent modification of the method described. That is, by the use of two microphones, double amplifier, and an electron switch it is possible to photograph or observe two chest sounds simultaneously on a single cathode ray tube. This makes more precise study possible but at the present time we have not used this method sufficiently to delimit its actual value.

The areas studied were located by external landmarks and the following system was adopted for location: the notation RP–T6–7 cm. means a point on the right side posterior at the level of the sixth thoracic spine and 7 cm. from the midline. In the back the level is referred to the spinous process. Distances are measured at right angles to the spine. In front we have followed the ribs laterally. Thus LA–T4–10 cm. means a point on the left side, anterior, and 10 cm. from the midline along the fourth rib. Various abbreviations have been used which are familiar such as "MCL" for midclavicular line, and "PAX" for posterior axillary line. The contact button of the Shure microphone is 0.75 inch in diameter so that it has not been necessary to make a distinction between ribs and interspaces. For more accurate vertical localization the symbol "$\overline{T4}$," i.e., with a bar above means the interspace below the fourth rib, while "$\underline{T4}$" means the interspace above the fourth rib. This method of location has proved practical in use.

Although the film record can be studied directly it is convenient to transfer the wave forms to a 14 by 17 inch sheet of paper by using a light box and locating the wave forms in the approximate position on a body outline. (Figure 3.) Direct tracing with this size sheet avoids crowding and the wave forms can be traced quickly. In some cases where the chest was deformed the camera was used to photograph the body outline and this outline was enlarged and projected onto the sheet for the outline. The distortion of chest radiographs makes it undesirable to attempt to superimpose the wave forms onto a chest plate.

Material Studied

Electrostethographic studies were made on 10 normal subjects and 22 patients from the University Hospital and Dispensary. In all about 1500 photographs were made. The cases were studied by the Medical Department and in addition were reëxamined by one of us. Roentgenograms were made in all cases within 24 hours of the time the electrostethographic studies were made.

Discussion

Figure 3 illustrates the types of wave forms observed in a normal male, and figure 4 is a grouping of wave forms from different chest areas in five normal males. In the upper chest the wave form comprises the fundamental frequency and an extra wave midway between. This is apparently an octave or first harmonic. The amplitude of the wave form is usually greater at the right apex than the left. Going down the back there is a progressive disappearance of this harmonic and at the bases of the lungs the wave form is a sine wave. The lower borders of the lung can be defined sharply by the sudden reduction in amplitude. Behind the heart on the left

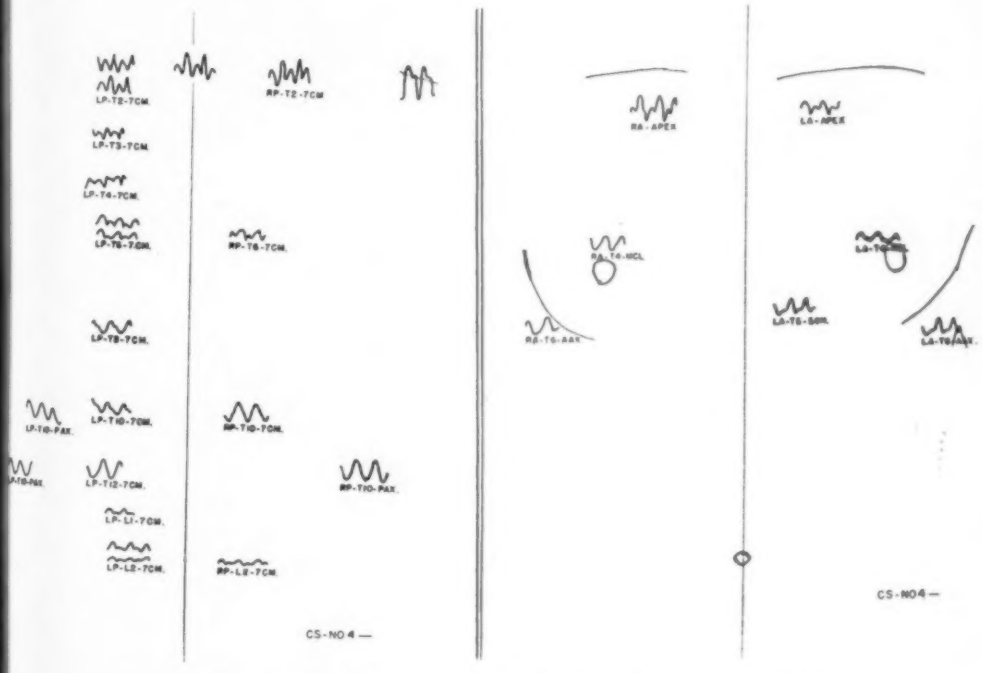

Fig. 3. Wave forms observed in a normal chest by the phonation method.

side there are characteristically remnants of harmonics present which are not present at the symmetric point on the right side in the normal. Occasionally, in the normal, higher harmonics are seen at the apices and these are more commonly on the right than the left. If the subject phonates loudly and harshly these may be conspicuous. Transmission of harmonics extends further down over the spinous processes than it does laterally to the spinal column. If the microphone settings are made 5 to 7 cm. lateral to the spinal column there will be more harmonic components on the left back than the right. Farther laterally, the wave forms are essentially similar except for the heart area previously noted.

In front there is excessive transmission of harmonics in the upper portion of the sternum. The wave form in the area of the heart in front is variable. In some cases there is a sharp reduction in amplitude, in others there is a marked change in the harmonic content, while in others there is little change until one is well into the superficial cardiac dullness.

In pneumothorax CS 28 an injection of 300 c.c. air reduced the amplitude at the posterior apex on the injected side 70 per cent as compared with a

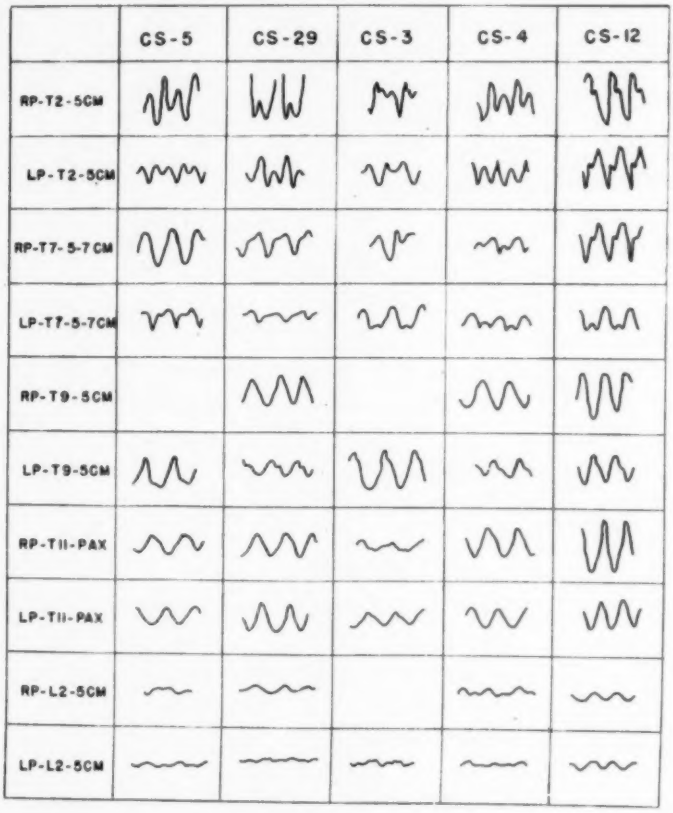

FIG. 4. Grouping of wave forms in five normal males to indicate the types of variations observed.

difference of only 10 per cent before injection. (Figure 5.) At LP–T3–5 cm. the reduction was 75 per cent, at T5–5 cm., 78 per cent, and at T7, 70 per cent. At LP–T5 posterior axillary line the reduction was 70 per cent as compared with symmetric points on the opposite side. Our experience would indicate that in the absence of adhesions there is a simple loss in amplitude. With adhesions there can be a marked increase in amplitude and persistence or alteration of harmonic components, with the appearance of abnormal wave forms, i.e. waves not seen in any area of the normal chest.

Hydrothorax when uncomplicated by adhesions results in a loss of transmission as shown in CS 32. (Figures 6 and 7.) Radiologically, at the time of the first electrostethograms the left chest was almost entirely opaque. Reductions in amplitude amounted to as much as 90 per cent. Later, when the radiological appearance showed the upper third or half to be partly cleared, the differences in amplitude compared with the normal side, amount to 40 to 50 per cent. There was no evidence of adhesions in this case and the fluid was an inflammatory non-tuberculous exudate with a specific gravity of 1.018. However, aside from the reduction in amplitude on the hydrothorax side many of the wave forms were abnormal in harmonic content.

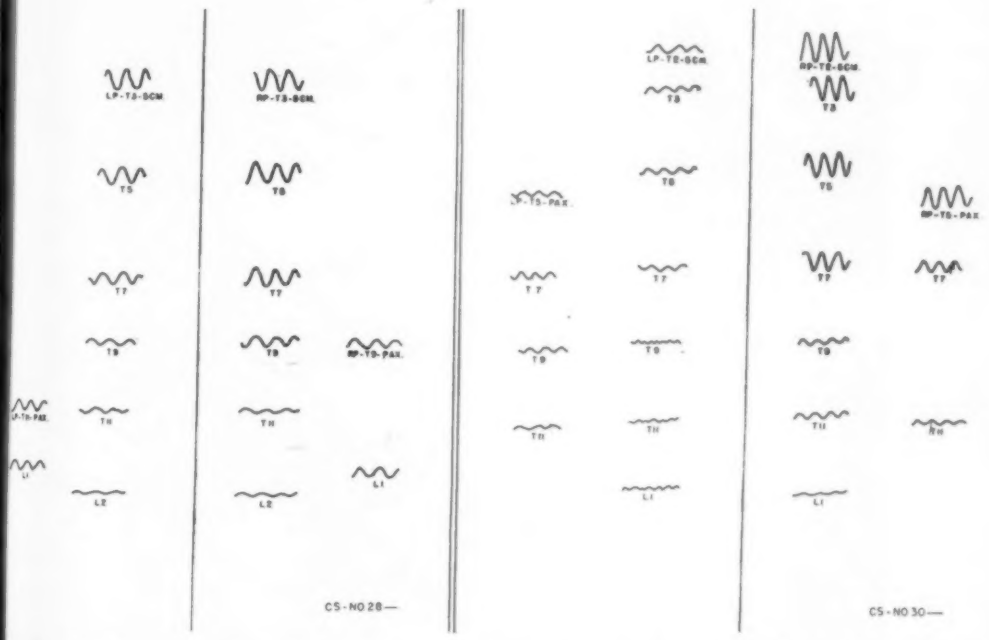

FIG. 5. Case CS 28, pneumothorax. Left chart is wave forms observed over back before injection of 300 c.c. air. Right chart is after injection.

CS 24, with fluid at the right base, showed numerous abnormal wave forms. (Figures 8 and 9.) After withdrawal of 1500 c.c. of transudate the wave forms were still markedly abnormal but there were alterations in the wave form corresponding to the radiological evidence of lowering of the fluid level. These consisted of phase reversals and changes in harmonic amplitudes. After removal of a portion of the fluid the roentgen-ray showed a dense adhesion which autopsy later revealed as dividing the pleural space into a lower and an upper cavity. The interpretation of the complex wave forms obtained at the right base in CS 24 is obscure at present but in comparison with the normal their abnormality is grossly apparent.

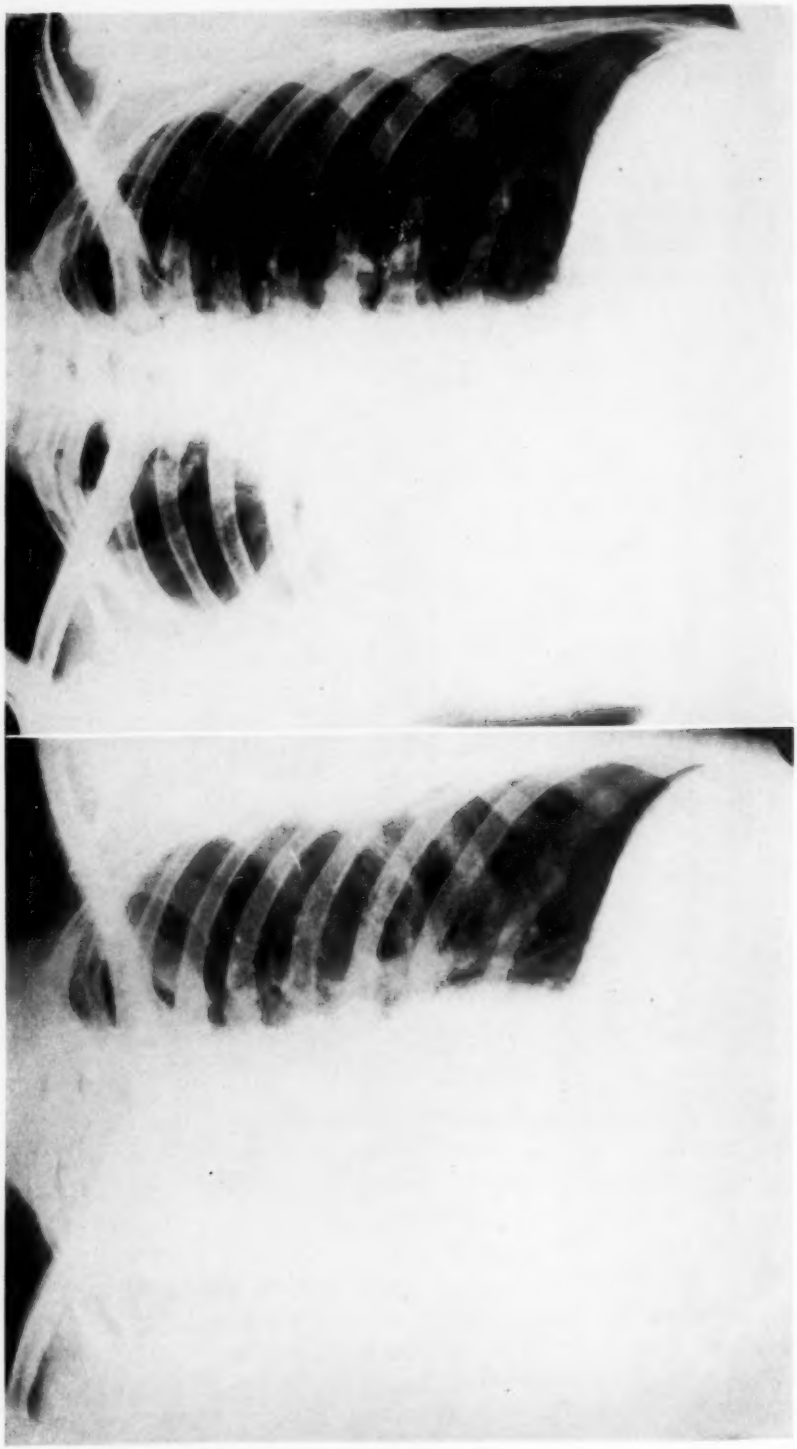

FIG. 6. Case CS 32, pleurisy with effusion. Radiographs (left) at time of first studies, and right at time of second studies.

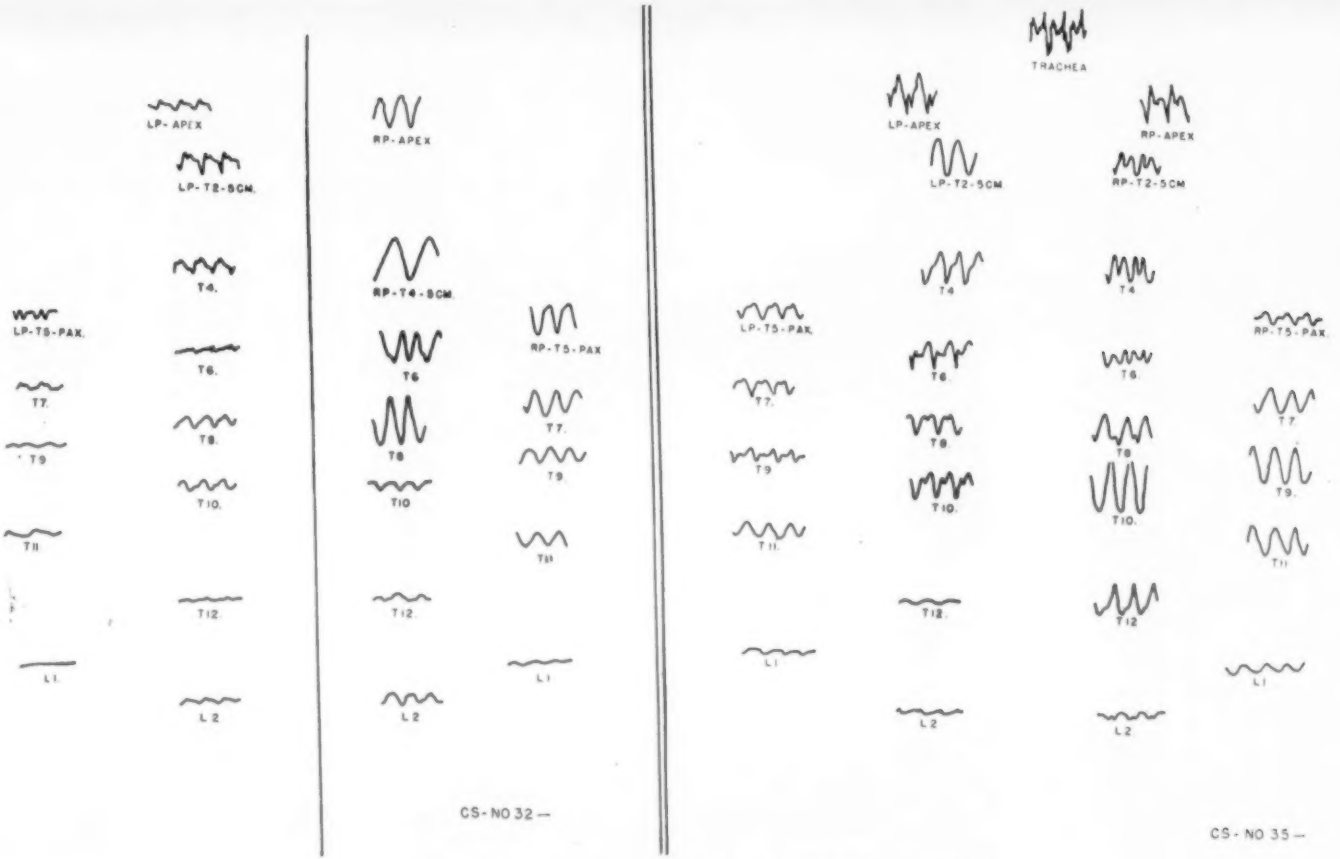

FIG. 7. Electrostethographs observed in case CS 32 (figure 6).

Both case CS 24 and 32 showed abnormal waves on the normal side of the chest. In CS 24 there was a marked increase in the size of the heart with some shift to the left but in CS 32 the roentgenogram was normal. The abnormalities consisted of (1) harmonic transmission in areas in which it is normally absent, (2) unusual variations in amplitude, and (3) the occasional appearance of large amplitude sine waves. These large amplitude waves also occurred in radiologically normal lung in CS 21, a man with a carcinoma of the lower half of the left lung. We have observed them elsewhere and wondered whether they might not be an expression of regional emphysema.

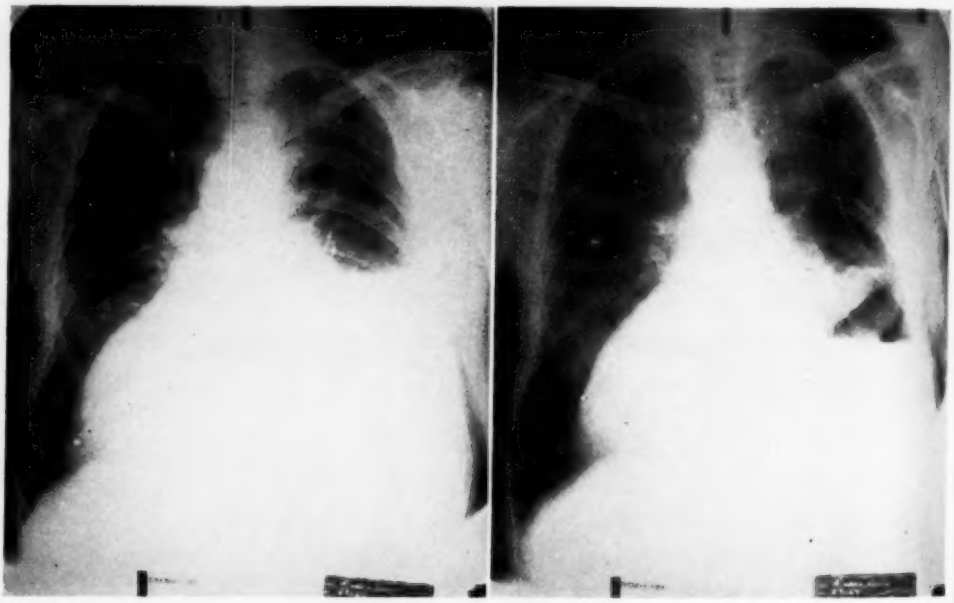

FIG. 8. Case CS 24, radiographs before (left) and after (right) thoracentesis in a case of right hydrothorax with chronic myocardial failure.

Cases CS 6 and CS 21 were studied because of healed fibrotic apical lesions. Case CS 6 showed a marked transmission of multiple harmonics to the apical area. He had a well-marked tracheal deviation from fibrotic contracture. Case CS 21 had an apical fibrosis confined to the apical tip without tracheal deviation. The amplitude was increased 300 per cent in the supraclavicular area as compared with the normal side. The subclavicular electrostethograms were essentially the same on the two sides.

Two cases of disseminated lesions showed abnormal harmonic components scattered throughout most of the chests. Case CS 23 was proved to be miliary tuberculosis at autopsy while CS 26 was identified as actinomycosis originating in the jaw. Our studies in pneumonia have been in-

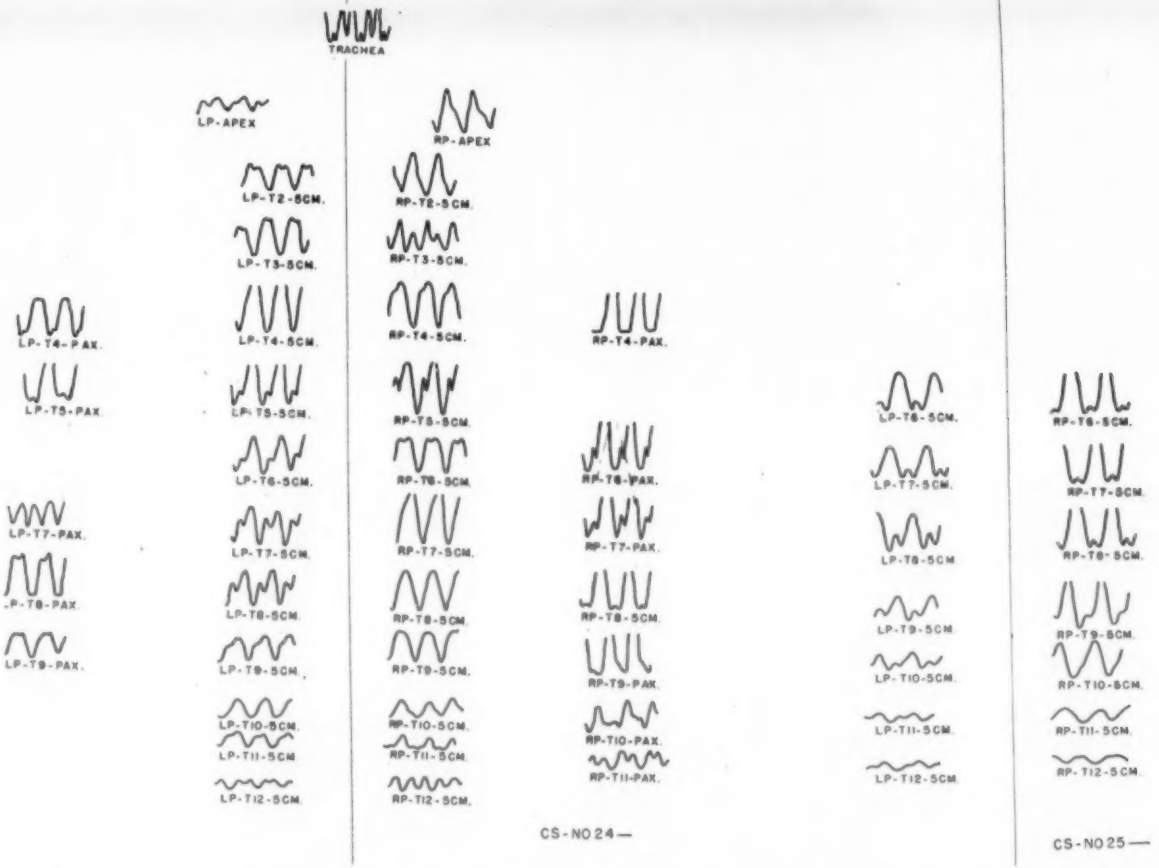

FIG. 9. Case CS 24, electrostethographs before (left) and after (right) thoracentesis. Note the marked abnormality of the wave forms and the inversion of the flat-topped waves after removal of fluid.

decisive because of current therapy and the lack of adequate radiographic study. We have not been able to study lobar consolidation although Wheeler using our equipment has observed increased amplitude and harmonic transmission.[8]

As noted before, the tenseness of the muscles affects the wave form somewhat, increasing the harmonic content. The amount of excess fat does not appear to be a handicap. In Case CS 34 after a radical amputation of the left breast six years previously, the wave forms did not appear to be materially altered although there was some increase in amplitude on the amputated side.

We have not yet been able to study the effect of diffuse pulmonary or peribronchial fibrosis unless it appeared as a complicating factor from chronic heart failure in case CS 24.

In our discussion we have interpreted the wave forms observed in terms of transmission of sounds from a source comprising those factors involved in voice production. When one compares the electrostethogram obtained at the side of the larynx with those obtained in the chest, the losses in transmission are readily apparent. However, when one encounters some of the complex wave forms observed in the lower parts of the chest in cases of empyema with carcinoma, in bronchopleural fistulae, and in old empyemas, etc., it seems necessary to consider the possibility that some of the harmonic components are formed by reverberation or echo phenomena either in air spaces or in tissues capable of acting as vibrating masses.

Martini and Mueller reported in 1923 the " free periods " of vibration of air in portions of the bronchial tree.[7] These periods of " free vibration " were determined in freshly isolated lungs using a mirror tambour method and at low energy levels in their studies on bronchovesicular breathing. We have not studied the frequency of the breath sounds at different areas of the chest although it is readily observable by increasing the gain of the amplifier. The frequency can be estimated visually but photographic records would of course require a moving film camera. The resonating frequencies may be distinctly different at the relatively high energy levels obtaining during phonation and the normal blood supply in the normal lung tissue may well alter the frequency relationships observed by Martini and Mueller. With the equipment available today their work should be repeated. If the frequencies determined by Martini and Mueller are approximately correct for intact lung (and Fahr's clinical observations would imply this), then from our observations we doubt whether the " free vibration " contributes materially to the electrostethograph record in the normal by the phonation method. However, in the presence of hydrothorax or adhesions, or the conglomerate types of masses occurring in carcinoma, bronchial abscesses, etc., the marked abnormality of wave form already observed by us, including in particular the flat-topped waves, may well be due in part to multiple vibrating systems operating at forced resonance levels. This would be anal-

ogous to the square wave formation observed in overloaded vacuum tube circuits, the wave form being produced by excessively rich harmonic oscillations.

Summary

1. An electrostethograph has been described utilizing a crystal microphone with mechanical contact, an electron amplifier and cathode ray tube recorder with a wide and uniform frequency response. By application of various improvements in design the apparatus except for cameras can be enclosed in a small case weighing less than 15 pounds.

2. Utilizing phonation and a sweep circuit the method permits visual study of chest sounds as well as single photographic exposures.

3. In the normal the characteristic wave forms observed in the upper chest comprise a fundamental frequency and an harmonic. These undergo progressive changes becoming sine waves at the lower border of the lungs. The lung borders can be accurately outlined. Behind the heart on the left the wave forms show differences as compared with the symmetric area on the right.

4. Changes in wave forms observed in a few pulmonary diseases have been described.

5. The phonation method described offers definite refinements in the study of chest sounds. Simplicity of operation and compactness make the method a practical one for the study of clinical patients.

We wish to express our appreciation to Drs. H. B. Hunt and J. P. Tollman and the Radiological Department of the University of Nebraska College of Medicine for assistance in correlation and for space, and to Rahm Instruments, Incorporated, 12 West Broadway, New York City, for technical aid in the design of the apparatus used.

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LIVER FUNCTION IN MENSTRUATION *

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While studying the excretion of hippuric acid in pregnancy Hirsheimer (1935) has shown that elimination of hippuric acid after administration of sodium benzoate is diminished towards the termination of normal and toxemic pregnancies, results confirmed later by other authors. The present investigation was undertaken to find whether the hepatic function during the menstrual period varies consistently from that recorded in the interval.

For this purpose we used Quick's test, based on the ability of the liver to detoxify benzoic acid by conjugation with glycine to form hippuric acid. First devised by Quick (1931), this test has been used sufficiently to give a fairly good idea of its value. The method is simple and consists of a gravimetric determination of the total hippuric acid in the urine for four hours after the oral administration of a dose of sodium benzoate. According to Snell (1935), this test gives reliable information as to the degree of hepatic damage present as shown by his studies at operation and necropsy. The test measures the amount of hepatic tissue able to build glycine; the amount of glycine available for conjugation with benzoic acid determines the quantity of hippuric acid eliminated in the urine. The less the liver tissue participates in glycine production the less can hippuric acid be synthesized.

Quick (1936) has worked out normal variations in the hepatic efficiency in men; the values range from 80 to 120 per cent. Pathological variations have also been studied by him especially in jaundice, cirrhosis, hepatitis and cancer; many papers have been published since, confirming Quick's investigations and applying them to different clinical purposes. Our attempt to ascertain whether variations of hepatic function occur during the menstrual period was executed in the following way:

Experimental

The subjects selected were 17 healthy women, students of the Mysore University Medical College and some staff members of the Krishnarajendra Hospital, all having normal menstrual history. Their ages varied from 19 to 35 years, the majority being from 22 to 24 years of age. All the subjects were subjected to the Quick liver efficiency test on two occasions, one being on the thirteenth to fourteenth day of the menstrual cycle, the other within 8 to 16 hours after the onset of menstruation.

* Received for publication June 2, 1941.

Method

For 24 hours previous to the test, the subjects were asked to avoid excessive consumption of vegetables, fruits, drinks, and to abstain from any tonics or drugs. On the subsequent morning at 6 o'clock the subjects were allowed a light breakfast consisting of a small cup of plain milk and two pieces of toast without butter. One hour after the light breakfast, 6 grams of sodium benzoate dissolved in 30 c.c. of distilled water were given; this was im-

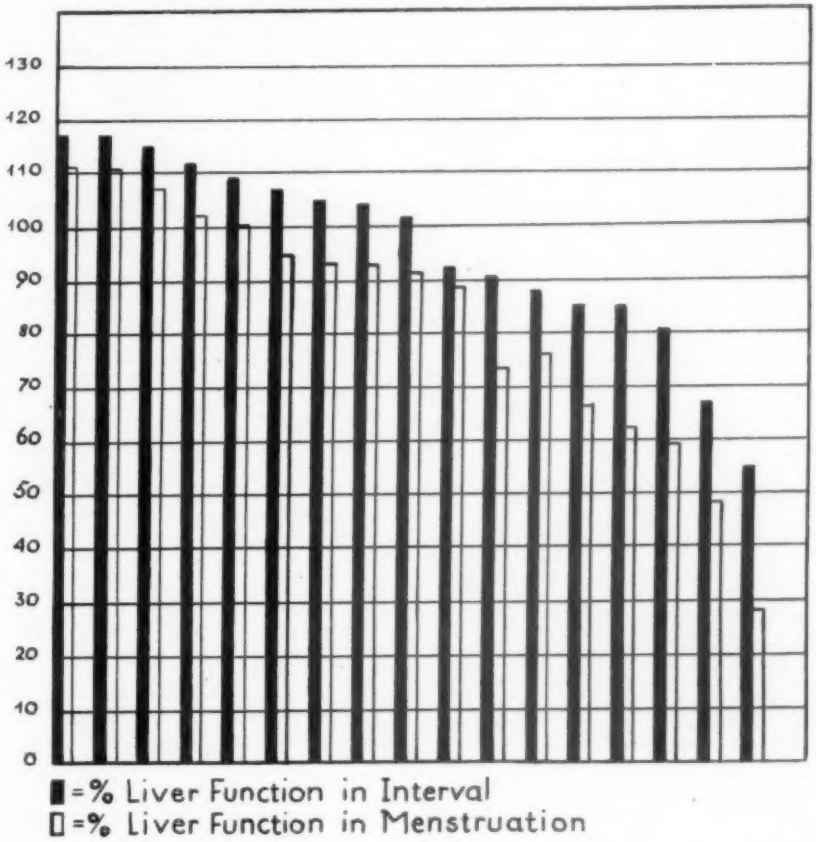

Fig. 1. This figure gives a comparative idea of the efficiency of the liver both at the interval and on the first day of the menstruation.

mediately followed by a drink of 120 to 150 c.c. of water. Immediately before taking the drug, the bladder was emptied completely and then complete specimens of urine were collected hourly for four continuous hours. Until the last sample of urine was collected the subjects were rested on a chair, and allowed to spend their time in reading light literature, as they complained of giddiness and weakness if they moved about, particularly when

the test was made on the first day of menstruation. The hourly samples were pooled, and half the total volume was taken for estimation immediately, the other half being reserved for a duplicate experiment to check the results. The sample of urine was acidified with 1 to 2 c.c. of dilute acetic acid, and

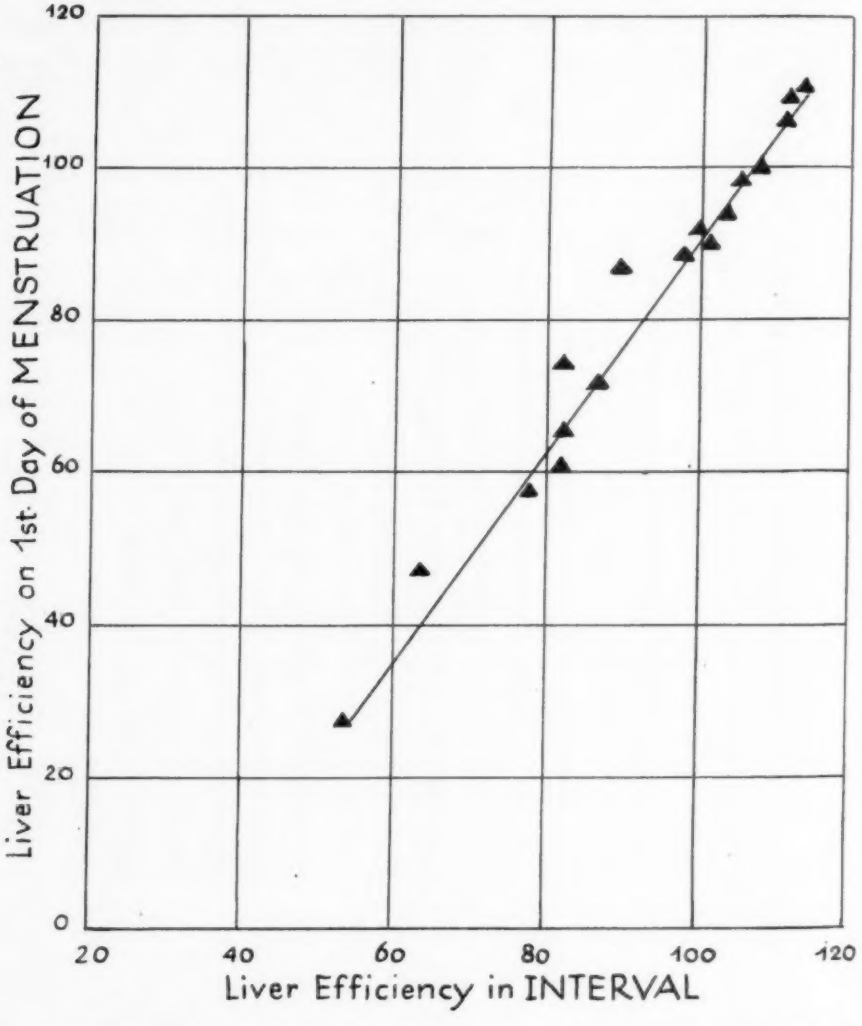

FIG. 2. The function of the liver on the first day of menstruation and during the interval. From the graph (figure 2) it can be seen that by studying the function of the liver, either at the interval or on the first day of menstruation, the function of the liver at the other period could be read with a variation of 2 to 3 per cent.

concentrated on an electric boiling water bath until the final volume was reduced to 20 to 25 c.c. The concentrated urine was well cooled and acidified with 1 to 2 c.c. of concentrated hydrochloric acid until the sample gave an acid

reaction to congo-red paper. Hippuric acid was allowed to crystallize out at the laboratory temperature. The crystalline hippuric acid was collected on a fluted filter paper and washed frequently with a small quantity of cold water.

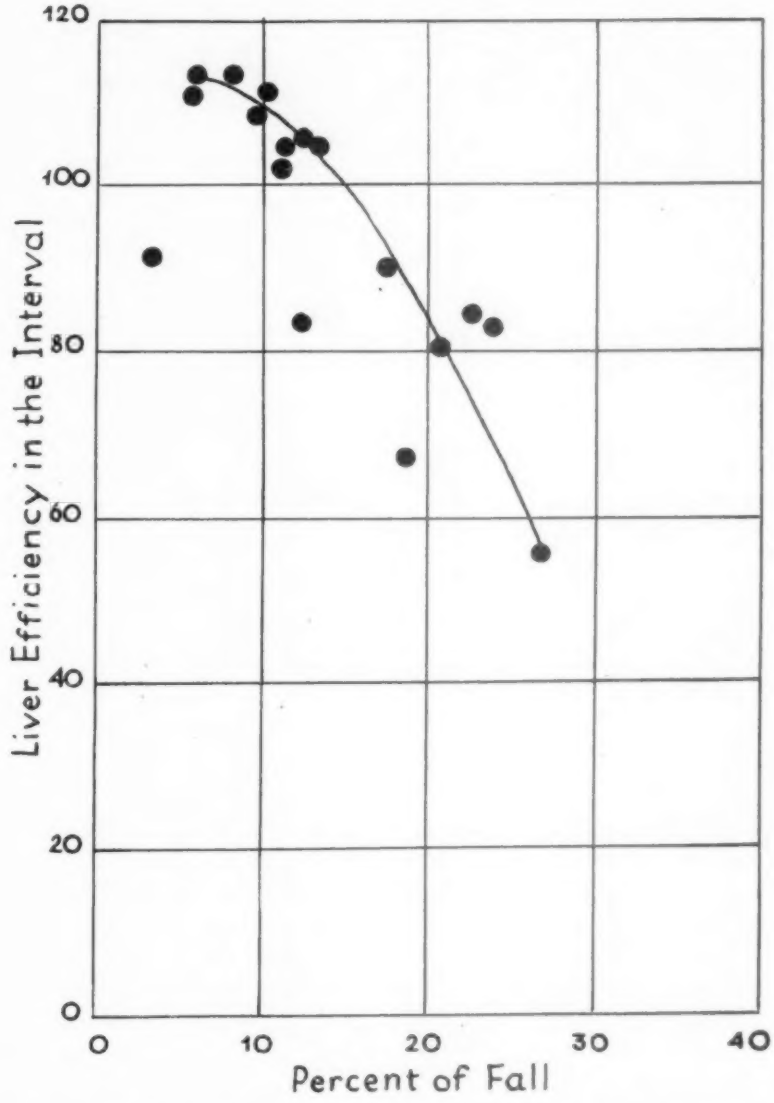

FIG. 3. The percentage of fall in the efficiency of the liver. From the curve it is seen that the percentage of fall was greatest in cases where the original function of the liver was at the lowest level.

The total volume of the filtrate was measured in order to apply the solubility correction of 0.33 gram per 100 c.c. of the filtrate at 25° C. to 26° C. The crystalline hippuric acid was dried in an air oven at 70 to 75° C. and weighed

to constant weight. In cases where the urine was contaminated with menstrual blood, hippuric acid was recrystallized from alcohol and weighed. In a few cases the melting point of the samples obtained was determined to test the purity of the sample; the melting point varied from 184–186° C. In a few cases estimations were made with hourly samples to study the rate of elimination of the hippuric acid. To express the results in terms of benzoic acid, the figure for the weight of the hippuric acid obtained was multiplied by the factor 0.68. According to Quick, a normal adult will excrete 3 grams of benzoic acid in the form of hippuric acid in four hours, the normal range varying from 80 to 120 per cent of this amount.

To eliminate disease of the kidney and hypertension, which may affect the result, the blood pressure was recorded, and an examination of the urine was made in all the cases.

The accompanying table (table 1) gives the result of the efficiency of hepatic function in women, both at the interval and on the first day of menstruation.

Results

The mean average of liver efficiency in the cases recorded was 95.72 per cent with a maximum of 117 per cent and a minimum of 56 per cent in the interval. From the results obtained, it could be seen that the function of the liver was lowered in the menstrual period compared with that recorded in the interval. The fall was nearly constant in subjects whose liver efficiency in the interval ranged from 95 per cent to 110 per cent. The variation in hepatic function was very small in cases where the liver function in the interval was over 110 per cent. A marked fall was observed in cases where the liver function at the interval was less than 90 per cent the degree of fall depending upon the original liver function; the lower the function of the liver in the interval, the greater is the fall during menstruation.

In one case (case 5), the liver efficiency on the first day of menstruation was as low as 28 per cent which may be pathological. The clinical examination of the subject showed no signs of impaired health, especially no symptom of liver, kidney, heart or lung disease, or of diarrhea. The amount of hippuric acid collected in the third and fourth hour was 0.94 gm. According to Hirsheimer it is interpreted as normal when the output for one hour is found to be 0.90 gram or more, and such interpretation is necessary by the possibility of delayed absorption of sodium benzoate, though assimilation is usually rapid.

Discussion

Our investigations prove beyond doubt that the liver function estimated by Quick's test is substantially impaired on the first day of menstruation. In the literature given in the Quarterly Cumulative Index Medicus 1931 to 1940, no references to examinations of the influence of the menstrual cycle on the

TABLE I

Serial No.	Name	Age	Diet	Blood Pressure	Pulse Rate	Pulse Pressure	Interval		First Day of Menstruation		Percentage of Fall	Amount of Fall %	Urine Exam.	General Remarks
							Hippuric Acid gm.	Liver Efficiency %	Hippuric Acid gm.	Liver Efficiency %				
1	H	35	M*	125/80	86	45	4.641	105.30	4.06	92.25	12.39	13.05	Nothing abnormal	European
2	K	24	V†	122/80	84	42	3.95	89.50	3.20	72.68	18.79	16.82	-Do-	Hindu
3	Mb	22	V	115/65	108	50	4.81	109.00	4.41	100.00	8.56	9.00	-Do-	Hindu
4	Mh	20	M	130/80	116	50	4.73	107.20	4.20	95.20	11.19	12.00	-Do-	Mohammedan
5	St	20	V	104/74	72	30	2.43	55.08	1.25	28.44	47.28	26.64	-Do-	Hindu
6	L	22	V	115/70	70	45	2.91	66.00	2.13	48.42	26.64	17.58	-Do-	Hindu
7	G	22	V	117/82	76	35	4.54	101.00	4.34	90.66	10.21	10.34	-Do-	Hindu
8	Sch	30	M	—	—	—	5.16	116.96	4.92	111.52	4.65	5.44	-Do-	European
9	V	20	M	100/70	76	30	4.05	91.80	3.93	89.08	2.96	2.72	-Do-	Indian Christian
10	SS	24	V	—	—	—	5.16	116.96	4.91	111.06	5.0	5.90	-Do-	Hindu
11	Rb	21	M	108/70	95	38	4.59	104.04	4.10	92.96	10.65	11.08	-Do-	Hindu
12	Sn	19	M	116/75	92	41	3.52	79.89	2.60	59.00	26.15	20.89	-Do-	Hindu
13	Sb	21	V	124/76	90	48	3.76	85.23	2.73	62.00	27.26	23.23	-Do-	Hindu
14	Rm	24	M	—	—	—	4.94	111.97	4.49	101.77	11.47	10.20	-Do-	Hindu
15	Abai	26	V	—	—	—	5.08	115.15	4.72	107.20	7.42	7.95	-Do-	Hindu
16	VK	24	V	—	—	—	3.75	85.00	3.30	75.00	12.00	10.00	-Do-	Hindu
17	Kbai	27	M	—	—	—	3.85	87.27	2.96	67.00	25.30	20.27	-Do-	Hindu

* M = Mixed food.
† V = Vegetarian food.

liver function were found. But there are other ways to show that our results are in accord with the facts established about physiological changes connected with menstruation. H. Küstner and Heilig have proved that the carbohydrate metabolism is deeply influenced by menstruation, results confirmed later by Eufinger. Heilig has shown that 100 grams of dextrose given orally on an empty stomach increase the blood sugar far more during the first two days of menstruation than in the interval; as the hypoglycemia following the alimentary hyperglycemia is well expressed also during menstruation, the abnormal high blood sugar values are most probably not due to pancreatic insufficiency. Srikantia et al. found definitely higher fasting blood sugar during menstruation than in the interval. Heilig suggested a reduced glycogen fixation in the liver as an explanation of these facts. It is further known (Heilig, 1924), that the water and chloride elimination is reduced up to 50 per cent during menstruation, compared with the elimination in the interval by the same healthy test persons, results being confirmed by Eufinger and Spiegler and by Thorn et al. and reproduced by injecting ovarian hormones (Thorn and Emerson). The fundamental investigations of the Viennese pharmacologist E. P. Pick (Molitor and Pick and Mauthner and Pick), confirmed clinically by Adlersberg and Minibeck, leave no doubt that the liver is one of the main regulators of water-chloride elimination. As no sign of primary kidney damage due to menstruation is known, Heilig suspected the liver of being responsible for water-chloride retention in menstruation. As normal liver function is essential for sufficient glycine synthesis, which also is the condition for normal Quick test, glycine being required to transform the benzoate to hippuric acid, the facts mentioned before make it probable that the diminished hippuric acid output on the first day of menstruation is due directly to a diminished liver function. The question arises whether also extra-hepatic factors may influence the hippuric acid elimination.

As menstruation is due to, and is accompanied by a profound change in endocrine correlations, it is most probable that our results are a further clue to hormonal regulations of this partial liver function. Bartels and Perkin and Boyce and Fetridge proved by Quick's test that hippuric acid elimination is impaired in hyperthyroidism. We do not know whether the thyroid function varies regularly with the menstrual cycle, though clinical experience and experimental facts seem to make it probable (Sherwood). We intend to investigate this question and further to see whether Oestrone or Progesterone has a measurable influence on the results of Quick's test.

Further it is well known that the tone of the autonomic nervous system or the balance between the cholinergic and adrenergic systems is distinctly changed in menstruation in the sense of a cholinergic preponderance due to an increased choline content of the blood in the first days of the menstrual cycle (Sieburg and Patzschke). Harpuder has proved, partly in confirmation of previous investigations, that adrenalin increases, ergotamine—the sympathetic depressor—diminishes substantially hippuric acid elimination; sympathetic

depression means automatic stimulation of the cholinergic branch; menstruation, being accompanied by hypercholinemia, shows among other signs of "vagus stimulation," also diminished hippuric acid elimination. Whether the liver function is influenced by choline directly or by a change in the ionic balance is not known. As a last possibility that factors other than the liver may influence our results, we have to mention the part that the kidney plays in hippuric acid synthesis (Snapper and Grünbaum, 1935). We see no practical way to decide whether this "non-excretory" kidney function suffers in menstruation, but it seems most improbable that such differences between interval and menstruation, as shown in our figures could be due to an impaired renal benzoic acid-glycine conjugation.

Far from underestimating the liver specificity of Quick's test—supposing the kidney function to be normal—we believe that apart from a primary depressed glycine synthesis, influences of the autonomic nervous system and probably endocrine factors have to be considered in explaining our results.

Summary

Quick's test was used to compare the liver function of 17 healthy women on the first day of menstruation with that in the interval.

Different possibilities are discussed to explain the impaired liver function in menstruation.

We wish to record here our thanks to the women students of the Mysore University Medical College and the Staff of the Krishnarajendra Hospital, Mysore, who offered themselves as subjects for experimental work, without whose willing coöperation this investigation would not have been possible.

Our sincere thanks are especially due to Dr. C. Srikantia, B.A., D.Sc., Professor of Chemistry, Medical College, Mysore, for his kindness in giving us the laboratory facilities and sparing one of his assistants (Mr. N. L. Kantiengar) for carrying out this investigation.

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CASE REPORTS

ANURIA FOLLOWING HEMOLYTIC REACTION TO BLOOD TRANSFUSION; RECOVERY FOLLOWING SPLANCHNIC BLOCK *

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Mortality from blood transfusions has been variously quoted in the past as from 0.2 to 1 per cent. While today it is to be hoped that the rate generally has fallen even below 0.2 per cent, transfusion of blood unfortunately will probably always carry with it a certain fatality rate.

Where the transfused blood is *compatible* fatalities are only rarely reported and usually are due to the development of pulmonary edema. This is commonly ascribed to overburdening of the right side of a previously weakened heart. Still more rarely cerebral hemorrhage or embolism and pulmonary embolism may occur.

The commonest cause of fatality from blood transfusion is the introduction of *incompatible* blood. Here, rarely, death may be almost instantaneous due to multiple thromboses, including the capillaries. More rarely death may occur directly due to exsanguination because of the hemorrhagic tendency following a hemolytic reaction.[1] But by far the most usual fatal mechanism after the injection of incompatible blood is the comparatively slow and undramatic onset of renal insufficiency. Once established, such insufficiency, with its concomitant anuria and uremia, is always of the gravest import.

It will probably never be possible to gauge accurately the true incidence of such transfusion reactions or estimate their fatality rate, for, as opposed to the comparatively few reported cases, certainly a very large number of such fatalities have never reached the literature. Such cases are not published for many obvious and understandable reasons—mainly that of grossly culpable errors in blood matching. Then too, at times, there is utter failure of the clinician to recognize the true nature and etiology of certain "kidney deaths" which followed transfusions. Occasional reports show it has been the pathologist alone who suggested the correct diagnosis.[2] In the comparatively scant literature on such transfusion anurias the mortality rate reaches high figures. Thus, DeGowin [2] in a frank discussion of his cases quotes one recovery in seven. Bordley [3] in 17 cases compiled from the literature, cites 11 deaths.

Such high fatality rates in a condition unfortunate and tragic often by its very occurrence make us acutely aware of the ineffectiveness of the usually prescribed therapeutic measures. It would seem warranted, then, to stress any therapeutic approach which by trial appears to have been specifically helpful.

The following case is cited in which a very serious hemolytic reaction followed the transfusion of blood—not of a different, but of the homologous group.

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The serological aspects of this case, in which a new agglutinogen is designated, are completely covered elsewhere.[4]

Case Report

M. E. P., a 32-year-old male, was admitted to the Mercy Hospital on November 22, 1939 with a history of recurrent attacks of headache, chills, fever and backache, associated with a leukopenia. The attacks began in January 1937, when he was operated on in another clinic for a perforated gastric ulcer. Postoperative course was complicated by a pneumonia associated with a leukopenia of 3000. A transfusion was given and the white count rose, the patient improved and was discharged. However, about six months later the attacks of headache, upper respiratory infection, chills and fever recurred. Clinical study is reported to have revealed nothing but infected tonsils and adenoids, with a hazy right antrum. Absolutely no drug history could be elicited from the patient, his wife or physician which would link up with the leukopenia. The tonsils and adenoids were removed and the right antrum drained on November 9, 1939 but the attacks recurred unabated. Because there had been apparent improvement in the initial attack in January 1937 from blood transfusion, the patient, who belongs to Group A (and as has later been ascertained, Rh minus) was given a transfusion on November 25, 1939 of 200 c.c. of fresh citrated blood. The blood of this first donor was also Group A but it has been shown since that he is Rh plus. About an hour after the transfusion the patient had a chill slightly more severe than those he had been having on the previous few days. No hemoglobinuria was noticed. The temperature dropped to a subnormal level and remained so for a week. Two other transfusions were then given from a second donor on November 27 and 30 respectively. This second donor's blood was Group A, subsequently shown to be Rh minus. No untoward symptoms followed transfusion from this donor. The patient remained temperature- and symptom-free and left the hospital on December 7, 1939. Two days later, however, he was readmitted on the service of Dr. M. C. Pincoffs with the same complaints of fever, chills, etc. On December 12 he was given a transfusion of 200 c.c. of fresh, citrated blood from the first donor (Group A, Rh plus) who had given blood to him 28 days previously on November 25. Twenty minutes after the transfusion was completed there was a violent shaking chill and the fever rose to 104.2 degrees. Adrenalin 1 c.c. was given, divided into three doses 10 minutes apart. One hour after the transfusion the patient developed bleeding from the nose and gums. This bleeding with nausea and vomiting, the latter at times bloody, persisted for days. A few ounces of urine were passed which showed hemoglobin but no red cells and soon complete suppression followed. Blood samples showed hemoglobinemia. The bleeding time was over 100 minutes and venepunctures oozed for many hours. Coagulation time was 60 minutes plus. Platelet count 144,000 (normal 500,000). The temperature dropped to and stayed subnormal. Blood pressure was 102 mm. of mercury systolic and 60 diastolic (figure 1). Aside from the bleeding the patient felt "not much different than from his other chills." Therapy during the rest of the day was limited to the slow injection intravenously of one ampoule of Hartman's solution and small amounts of 5 per cent glucose. Fluids were given by mouth despite the vomiting.

Progress notes listed below present briefly the developing clinical picture and the therapy used.

Progress notes: 12/13/39: After passing 60 c.c. urine at 6 a.m. has been completely anuric. Persistent lumbar pain, nausea and bloody vomiting continue. Blood urea 77 mg. per 100 c.c. The patient is jaundiced and has prompt direct positive Van den Bergh of 3.9 mg. (This, several days later, turned to the indirect type and finally became negative.) As the precise serologic etiology of this homologous group

reaction was undetermined at this time, the therapeutic administration of "correct group blood" was impossible. Therapy: Forced fluids by mouth and intravenously—the latter mostly glucose. In addition small amounts of intravenous Hartman's solution.

12/15/39: Still anuric. No definite change or improvement in general condition. Drowsy but mentally clear. Blood urea 110 mg. per 100 c.c. (For blood and urine studies, see table 1.)

12/16/39: No change in status of patient, save that edema is developing in the face, over the sacrum and tibiae and ascites is present. Therapy: In addition to the daily intravenous glucose 300 c.c. of Sorbitol (a pentose sugar) were given very slowly intravenously. Diathermy to each kidney for 15 minutes.

12/19/39: Still anuric with increasing edema and ascites. Blood urea 100 mg. per 100 c.c. and creatinine 7.5 mg. per 100 c.c. Therapy: Continuance of intravenous glucose daily with intravenous Sorbitol on several occasions.

12/20/39: Patient voided 75 c.c. of clear orange brown urine coincident with an enema. (Urine: Sp. gr. 1.14; alkaline; albumin 4+ and benzidine test four +; no casts, occasional red cells.) Blood urea 128 mg. and creatinine 9.6 mg. Carbon dioxide combining power of the blood plasma has always remained normal.

12/21/39: The anuria persists with edema increased. Patient feels and looks worse. Blood urea 132 mg.

12/22/39: Anasarca has increased with signs of fluid at both pleural bases. A pericardial friction rub is heard. Diathermy this morning (now for the third time) with no appreciable effect.

Splanchnic block done at 2:45 p.m. by Dr. D. Pessagno, according to the technic of Labat.[5] Using 1 per cent novocaine, 40 c.c. were injected on each side, 25 c.c. in the region of the greater splanchnic and 15 c.c. in the region of the lesser splanchnic nerve. The procedure was done entirely retroperitoneally. The needle was inserted through the back lateral to the first lumbar vertebra on each side. Careful record of blood pressure showed only a comparatively slight drop immediately after the block and it returned to the preoperative level within 40 minutes.

Bladder dullness soon became evident and percussed increasingly higher until at 7:30 p.m. the patient voided 500 c.c. of dark orange urine following an enema. (Urine: acid; sp. gr. 1.010; albumin 3+; no casts, eight red cells per high power field.)

12/24/39: Average daily urine output around 1275 c.c. Edema greatly relieved. However, blood urea is 216 mg. per cent with creatinine of 9.4 mg. Because of the low blood and urine chlorides the intravenous glucose is given in saline and hypodermoclyses of normal salt initiated. There is less vomiting but patient is drowsy.

12/28/39: Patient is more alert and there is no nausea or vomiting. The blood urea and creatinine are falling. There has been so much diuresis (6000 c.c.) that despite the increasing edema fluids are still being forced to prevent hemoconcentration.

1/3/40: For the past several days patient has been able to take nourishing foods. Also oral fluid intake has risen and the blood urea has fallen to 48 mg. with creatinine of 1.9 mg. Rather marked waterlogging had occurred by 12/29/39 and due to a satisfactory chemical balance hypodermoclyses were stopped. The edema is now definitely decreasing.

From this point on there was progressive improvement of the patient to normal. The urine, which had constantly shown traces of albumin with many red cells since diuresis began, became normal. Phenolsulphonphthalein tests gave results as follows: (December 30, 1939) 12 per cent; (January 7, 1940) 37 per cent; (January 17) 53 per cent; (April 18) 75 per cent. The specific gravity of the urine for over a month after the reaction remained constantly fixed between 1.009 and 1.011. However, in

TABLE I

Studies During Anuria and Uremia

Date	Fluid Intake c.c.		Plood						Urine					
	Total	Intraven.	Urea	Urea N	Creat.	CO_2	Cl	NaCl	Time	Cl	Total Cl	Urea N mg. %	Total Ur. N	Quant. c.c.
12/11	3200		24	11										625
12/12	2450								(Hemolytic Transf. Reaction)					350
12/13	3555	2290	77	36		55								50
12/14	2525	1950	100	45	2.9									0
12/15	2665	2390	110	50	3.2	51								0
12/16	2795	2700	125	55	6.0	57								0
12/18	2475	2200	105	50	8.3									0
12/19	2310	2210	100	46	7.5	60								0
12/20	2515	2300	128	60	9.6	51								75
12/21	1445	1200	132	62		51								0
12/22	1225	1200							(Splanchnic Block)					500
12/23	1700	1650	100	46	10.0	46				133	1.7	156	2.0	1280
12/24	2750	2000	216		9.4	54	240	396	7a.m.–7p.m.	72	0.67	211	1.9	925
									7p.m.–7a.m.	72	0.25	149	0.5	350
12/25	3600	2450	224		10.8		270	445	7a.m.–7p.m.	84	0.36	178	0.8	450
									7p.m.–7a.m.	96	1.58	203	3.3	1650
12/26	4625	1850	250	115	14.5		270	445	7a.m.–7p.m.	96	1.0	180	1.9	1045
									7p.m.–7a.m.	156	1.68	238	2.6	1080
12/27	4975	2250	175	90	7.5				7a.m.–7p.m.	132	2.64	258	5.2	2000
									7p.m.–7a.m.	96	1.74	238	4.3	1820
12/28	4150	2350	115	55	4.4		270	445	7a.m.–12m.	192	3.7	328	6.3	1925
12/30	3150	2000	94	44	3.7		285	475	12m.–12n.	264	10.8	250	10.3	4100
									12n.–12m.	264	5.8	263	5.8	2230
12/31	3025	1500	72	33	3.3		320	528	12m.–12n.	300	5.8	250	4.8	1930
1/1	2500	1000												3975
1/2	2750	1000	52	24	2.0		340	561						2900
1/3	2250	0	48	22	1.9									2675
1/8	2525		45	21			290	478		240	4.6	301	5.8	1950
1/10	2875		37	17			280	462		900	23.4	243	6.3	2600
1/13	3000		41	19			190	311		276	7.3	205	5.4	2650
1/20	3160		32	15										2000
1/27	2200		23	11										2500
2/29			34	16										

three months' time the patient was able to concentrate to 1.032. A moderate anemia (Hb. 70 per cent; 10.5 grams) present after the reaction, with ferrous sulphate therapy was replaced by a normal blood picture.

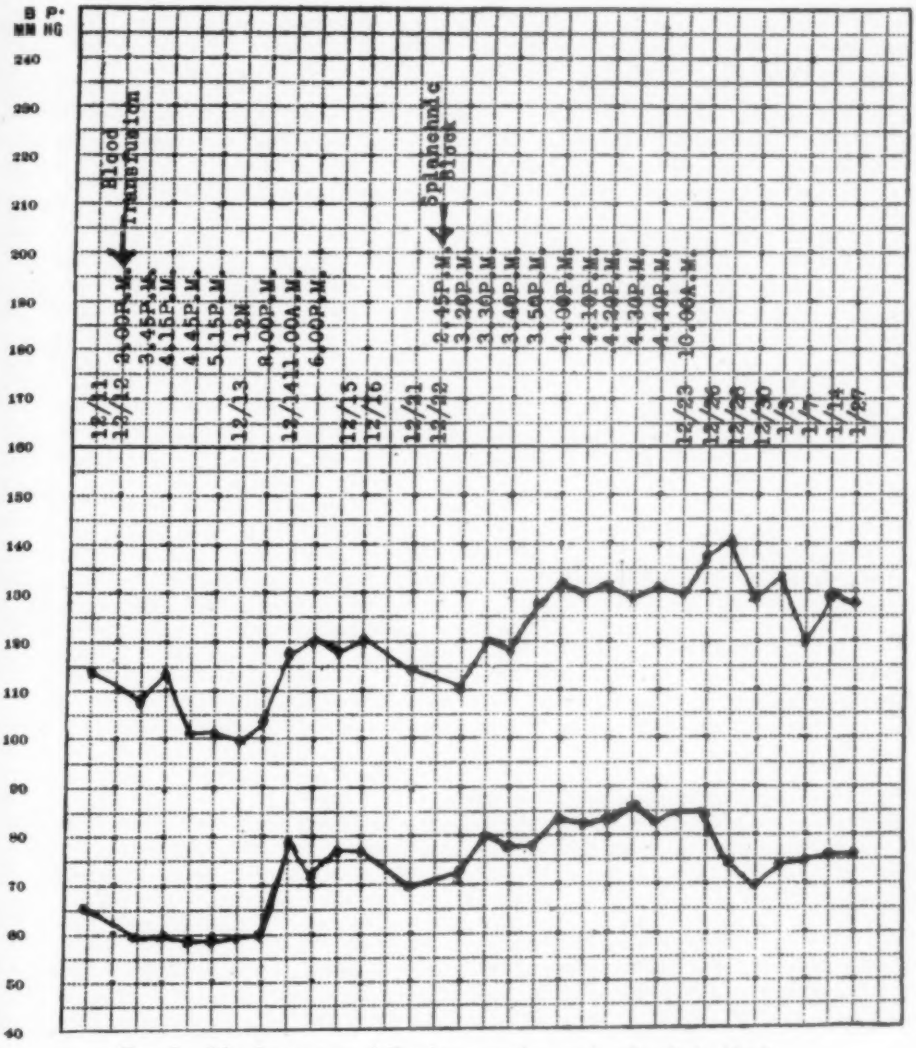

FIG. 1. Blood pressure following reaction and splanchnic block.

DISCUSSION

The mechanism involved in the suppression of renal function after hemolytic transfusion reactions is still not completely settled. There can be no doubt that the experiments of Baker and Dodds,[6] Yorke and Nauss,[7] Melnick et al.[8] and DeGowin et al.[9] show conclusively that precipitated hemoglobin does block the tubules in these cases, and, in the opinion of many, the whole picture of urinary suppression is thus solely and adequately explained. But, strangely, in a certain

proportion of fatal transfusion anurias such reported tubular obstruction, while present, has been notably sparse and quantitatively of a minor degree. Thus, DeGowin [2] commenting on the obstructive theory feels that "the principal objection to it is that in many human cases not enough pathological evidence of tubular obstruction can be found." Warner [10] likewise believes the pathology seen is "often not sufficient to explain the fatal uremia." Granting the part played by hemoglobin obstruction, evidence of further search for the complete mechanism involved is had in the variously proposed theories of chloride loss,[11] an allergic mechanism,[12] hemolytic nephrotoxic substances, etc. That these latter occur has also been seriously questioned.

There remains the by no means recent theory of *spasm of the renal vessels.* Mason and Mann [13] in 1931 injected intravenously into animals the stroma of laked red cells and produced no apparent effect on the vessels. But the injection of extracted hemoglobin from such cells produced a "specific vasoconstrictor action on the vessels of the kidneys." Hesse and Filatov [14] in 1933 obtained similar experimental results and later in the same year reported a hemolytic reaction in the human [15] due to grossly mismatched blood. They attributed the intense backache in this and similar cases directly to the local renal vascular spasm. They were able almost immediately to transfuse properly matched blood (for which therapeutic procedure they claim priority) and, according to them, this brought about instant relief of the pain and the patient suffered no ill effects from the transfusion.

It would seem from available pathological reports that the kidneys of patients dying of transfusion anurias often present points of similarity to the kidneys observed in the so-called "reflex anurias," in which latter vasoconstriction plays such an important part. Today reflex anuria, while rare, is acknowledged as a clinical entity by a great number of observers. A typical example is the complete bilateral suppression of urine in a patient with calculus obstructing one ureter. Innumerable such cases are reported and among other ascribed causes of reflex anuria are hysteria, blows over the kidney, exposure to cold, fractured vertebrae, perinephritic abscess, plastic peritonitis, etc. Rubritius [16] seems to have described the pathology of such kidneys quite thoroughly and accurately. He found that as opposed to former belief that the kidneys were pale and shrunken, reflex kidneys instead were "large, swollen and with full vessels." The vasoconstrictor action then would appear to be on the side of the efferent renal vessels, causing blood to stay pent up in the kidneys. Many continental writers have reiterated this belief and recently Cubitt,[17] describing the kidneys as "enlarged and deeply congested," concurs in the angiospastic pathogenesis.

It would seem worthy of note, then, that not only has renal vasoconstriction been experimentally produced by intravenous hemoglobin injection but in the comparatively few reported autopsies after transfusion anuria the kidneys are grossly congested and swollen. Thus, Wiener [18] declares the kidneys are usually found to be swollen with the pyramids appearing dark in color. Their vascular status, then, might well be analogous to that of the reflex kidney.

Experimentally, irritation of the splanchnic nerves has been shown to cause oliguria and conversely section or anesthetic block will cause prolonged polyuria. In addition no untoward effects could be ascertained after splanchnic section.[19, 20]

As early as 1922 a therapeutic effort was made specifically to combat the renal vasoconstriction in reflex anuria. Neuwirt [21] is generally credited with

having first successfully relieved such anuria by means of splanchnic block. Rubritius [22] reported success with this measure in seven out of eight cases. Haslinger [23] and also Havlicek [24] each quote reflex anuric cases in which splanchnic block initiated diuresis.

As an alternate procedure a few writers have advocated spinal anesthesia. Thus, Hayes and Paramore [25] report the production of diuresis by this method in a case of plastic peritonitis with reflex anuria. Cubitt [17] likewise tried spinal anesthesia in one case with success. Compared to splanchnic block this procedure has received little attention as is evidenced by Cubitt's statement that this treatment (spinal anesthesia) had not to his knowledge been previously described.

Splanchnic block in reflex anuria may have definite advantages over spinal anesthesia. The application of a large quantity of anesthetic solution directly to the splanchnic plexus may, by its undiluted state and its mechanical bulk and pressure, more thoroughly interrupt the sympathetic flow. According to Haslinger [23] the duration of splanchnic block would seem much longer than one would expect in spinal anesthesia. Rubritius [16] claims the possibility of peripheral "sub-station plexuses" creating reflex arcs of their own which necessitate a more peripheral, splanchnic block for their complete interruption. Then too, as in some cases fibers making up the splanchnic nerves arise from as high as the fourth dorsal segment,[20] a spinal anesthetic to be at all efficient, must be given rather high. Splanchnic block has never in our experience caused any appreciable fall in blood pressure. As fall in blood pressure is ascribed as a cause for some anurias,[26] certainly spinal anesthesia, with its greater incidence of blood pressure fall, may possibly at times partially defeat its own purpose in an existing anuria. Lassen and Husfeldt [27] in studying the effects of fall of blood pressure on the kidneys of normal individuals used spinal anesthesia to produce such fall and concluded that peripheral blood pressure need fall but a little below 70 mm. of Hg before production of urine could cease entirely. It would seem then that splanchnic block is the preferable procedure and in the hands of an experienced operator it is entirely innocuous.

Cognizant, then, of the vasoconstrictive similarity of the reflex kidney to the "transfusion kidney" splanchnic block is suggested as an added therapeutic measure against the latter. To my knowledge this particular procedure has not before been used in such anurias. The use of spinal anesthesia in a case of transfusion anuria has been reported by Johnson and Conway.[28] They saw no specific effect and, despite later diuresis, uremic death occurred. DeGowin [2] in reporting seven transfusion anurias used spinal anesthesia in one case—incidentally the only case which recovered. He notes, however, that the clinicians regarded the recovery as spontaneous.

It cannot be too urgently stressed that whatever, if any, value splanchnic block may possess in transfusion anurias, it should only be considered the key for unlocking the door to subsequent judicious treatment. The establishment of diuresis, while an essential step, far from insures recovery for the patient. Reference to figure 2 makes evident the very stormy period following diuresis in the case herein reported. Careful observation of the chemical balance of the patient may often clearly guide the treatment. The excellent advice of Cabot and Iber [29] and Jeghers and Bakst [26] regarding anurias can well be heeded here: The kidneys must have a continuously positive water balance. Hence, dehydra-

tion must be watched for, prevented or treated. As much as 5000 to 7000 c.c. of fluid daily can be lost in some cases by vomiting, diarrhea, gastric retention and by way of the lungs and skin—yet with no urine passed. Fluids then must be forced (often almost entirely intravenously) even up to 6000 c.c. or over daily. If intravenous injection is slow 'overburdening of the circulation' will not occur and even this danger is less than that of dehydration. As to the nature of the intravenous fluids judgment must be used. Saline is best to overcome dehydration for the sodium ion is necessary to fix the water to the tissues. In higher strengths, if necessary, it must be used to raise lowered blood chlorides. However, because saline is taken up by the tissues, it may not be as good in certain stages of an oliguria as glucose solutions, for the water of a glucose solution is more available for renal excretion. This is more true of hypertonic glucose. Both saline and glucose should be used, watching the chemical balance. Blood chloride and blood sodium levels do not always parallel each other. As pointed out by Jeghers and Bakst [26] few laboratories are equipped to perform routine sodium determinations. However, they add "indirectly, the sodium level can be roughly surmised in many cases from a comparison of the blood chloride level and the carbon dioxide combining power. If the carbon dioxide combining power is high (alkalosis) and the blood chloride level is low, then the sodium level is probably near normal. Conversely a low carbon dioxide combining power (acidosis) with normal or slightly low blood chloride level speaks for the presence of an hyponatremia." Since the kidneys, in the presence of an alkaline urine, readily excrete hemoglobin as oxyhemoglobin Baker and Dodds [6] advocate the giving of alkalies in treatment and this seems theoretically plausible. The carbon dioxide combining power should be watched, however, to guard against alkalosis.[30] Diathermy to the kidneys has had a few reported successes and many failures. Its value at any stage must still be proved. Transfusions of truly compatible blood have been advocated after a reaction due to mis-matched blood.[15] Under such circumstances the procedure should be considered provided one is sure of having truly matched blood at this stage. Decapsulation of the kidneys in any anuria is today in rather wide disfavor.[29]

Finally, it must be remembered that, no matter how successfully splanchnic block may relieve renal vasoconstriction, in any given case one may still have kidneys in which widespread tubular epithelial degeneration has developed and the prognosis must be judged accordingly. Early initiation of all the outlined therapeutic measures would seem of paramount importance.

Summary

1. A case is presented in which a hemolytic reaction and prolonged anuria developed following transfusion of blood of the homologous group. After failure of other measures for nine days, diuresis followed within a few hours after a splanchnic block and there was ultimate complete recovery of the patient.

2. Accrued evidence is offered in favor of a vasoconstrictive renal element in transfusion anuria similar to that of the so-called "reflex anuria." Splanchnic block would seem a preferable and innocuous measure against such renal angiospasm.

3. It is stressed that splanchnic block, even if successful in its purpose, is only "the key which unlocks the door" to further judicious therapy.

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EQUINE ENCEPHALOMYELITIS IN A LABORATORY TECHNICIAN WITH RECOVERY *

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SINCE Meyer's original report of equine encephalomyelitis in man,[1] many cases of this disease have been described in the medical literature. Excellent reviews have been published by Fothergill [2] and by Olitsky.[3] Recently a proved case of encephalomyelitis in a laboratory technician was reported by Fothergill, Holden, and Wyckoff.[4] It resulted in death and the virus (Western type) was recovered from the brain at autopsy. We wish to report another laboratory infection. Our case is interesting because we were able, fortunately, to determine the virulence of the infective agent, its portal of entry, and the incubation period. Moreover, the titer of antiviral protective antibodies present in the blood of our patient before infection occurred is also known. In addition, the clinical record was dramatized by the development of acute Parkinsonism. Finally, large doses of a specific antiserum of high potency were used intravenously, intramuscularly and intraspinally. Complete recovery ensued.

At the outset we wish to state that we have not formed any set opinion as to the value of the specific serotherapy employed in this case. We are well aware of the generally accepted belief, so aptly stated by J. E. Gordon,[5] that " Medicine has little to offer in respect to a specific attack on acute virus disease. Immunologic principle is opposed to success because once a virus has established itself inside the cells—and usually this occurs by the time symptoms are definite —little benefit can be expected from antibodies transported by blood or lymph and acting extracellularly, even though given in large amounts." However, in the absence of other means of treatment our experience warrants the use of a highly potent serum in large quantities if available. It may serve to limit the spread of the disease and thus aid in recovery.

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From the Medical Research Division, Sharp and Dohme.

Case Report

J. R., a white male, 29 years of age, came in contact with encephalomyelitis virus for the first time on February 8, 1939, when he was assigned to assist in experimental work in the encephalomyelitis vaccine division of the Mulford Biological Laboratories, Sharp and Dohme. His work consisted of inoculating eggs with the virus (Western type), removing the diseased embryos, and grinding them in a mortar. On March 2, 1939, he was transferred to duties connected with the preparation of the vaccine on a production scale, and thereafter assisted in harvesting and grinding the embryos in large quantities. Sterile gowns, caps, gloves, and masks were worn throughout the operation. Minor injuries and accidents were regarded by the personnel as serious and were reported promptly.

On April 3, 1939 samples of blood were drawn from J. R. and other members of the staff to determine the presence of neutralizing antibodies in their sera. Tests were done in duplicate by Dr. J. W. Beard, of Duke University, and by one of us (B. H.). The results were negative. Fifteen days later, April 18, 1939, at 3:50 p.m., while cracking a diseased egg * over the edge of a funnel, some of its liquid contents splashed into the patient's face, close to the right eye. He reported slight burning of the right eye. The patient immediately washed his face with 90 per cent alcohol and reported to the first aid dispensary. Examination by Dr. LeRoy Wenger failed to reveal any irritation of the eyes. Treatment consisted of thorough washing of the face with soap and water and instillation of a few drops of 10 per cent Cargentos (Protein Silver Mild) into the right eye which was flushed out before and after with boric acid solution.

The patient returned to work but reported to the dispensary on April 19, 20 and 21, when Dr. Wenger found no evidence of disease. On April 24, the patient did not report to work because of illness. Dr. Wenger called at his home and elicited this additional history: He had worked up to Saturday noon (April 22). During that morning the patient had noted pain in back of the forehead and between the temples. This became worse so that when he got home he went straight to bed and slept until Sunday noon (April 23). Severe headache was present on awakening. The family physician, Dr. H. B. Conaway, was then called in. A diagnosis of grippe was made and suitable medication ordered. Examination by Dr. Wenger revealed a coated tongue and some injection of the throat. No neurological abnormality was found. The temperature was 100.3° F., and the pulse 85.

The patient was reëxamined the next morning at 11 a.m. Severe headache was still present. At this time Dr. Wenger noted that the patient was slightly stuporous and had to be roused to get ordinary answers. Temperature was 102.2° F., and pulse rate was 100. The neck showed some stiffness. The arm and patellar reflexes were diminished. No other abnormal signs were found. At 2 p.m. the patient had 103.2° F. fever and a pulse of 120. After consultation with Dr. Conaway, who had

* The history of the virus with which this patient became infected is as follows: The Western type virus (Iowa 1937 strain) was received at the Mulford Laboratories from the Bureau of Animal Industry, Washington, D. C., in the seventh guinea pig brain passage. It was transferred once to guinea pigs and thence to chick embryos. Twenty-ninth chick passage material was being harvested at the time of the accident. On April 7, 1939, or 11 days before the accident, the twenty-seventh passage of this strain of virus had been tested on guinea pigs for infectivity by the subcutaneous route of inoculation. Young guinea pigs weighing 250 grams were used. Two pigs were injected with 0.1 c.c. each, two with 0.25 c.c., and two with 0.5 c.c. The material used for the guinea pig injections was simultaneously titrated on 21 day old Swiss mice by the intracerebral injection of 0.03 c.c. of serial dilutions in tenths. The 10^{-5} dilution killed mice; thus, 1 c.c. contained approximately 3,300,000 mouse intracerebral doses. All six guinea pigs developed marked symptoms of encephalomyelitis. One of each group died. The remaining three animals showed severe emaciation for six weeks, at which time they were destroyed. This observation indicates that the virus was highly infectious when injected peripherally.

independently verified the serious turn in the patient's condition, it was decided to hospitalize him for spinal fluid study. Upon his admission to the Roxborough Memorial Hospital of Philadelphia, on April 25, 1939, at 7:25 p.m., the attending resident, Dr. T. Greenspon, found marked rigidity of the neck, a bilateral positive Kernig sign (more marked on the left), and absent abdominal reflexes. The biceps, triceps, and patellar reflexes were normal. Babinski sign was negative. Although the patient was at times disoriented and quite stuporous, he answered questions with a fair degree of accuracy. The spinal fluid was faintly cloudy, under 14 mm. of mercury pressure, and contained 600 white cells. There were no organisms seen on direct smear. White blood cell count was 14,600, polymorphonuclears 88 per cent, lymphocytes 4 per cent, monocytes 8 per cent. Rectal temperature was 104° F., pulse 140, respirations 28. When one of us (H. G.) saw the patient for the first time at 9:30 p.m. he was found smoking in bed, very nervous and jumpy, and sweating profusely. A coarse tremor of the hands was noted. Skin and eye tests for horse serum sensitivity were negative. Dr. Sherman F. Gilpin of Philadelphia, a neurological consultant, saw the patient at 10:30 p.m. and confirmed the above findings except for a decrease in the reflexes of the arms. Sensation to pin-prick was apparently intact. The cranial nerves appeared normal. Throughout the examination the patient muttered in a delirium but was otherwise fairly coöperative. Dr. Gilpin agreed with our presumptive diagnosis of equine encephalomyelitis, and the specific therapy we proposed to use. In addition, he suggested the trial of sulfanilamide.

Five hundred fifty c.c. of antiencephalomyelitis immune horse serum * were then given intravenously by gravity method without any untoward reaction except for a few hives. Spinal puncture was repeated. A turbid fluid under 14 mm. of mercury pressure dropped out slowly. After removing about 40 c.c. of spinal fluid, 50 c.c. of the immune serum were injected intrathecally without any reaction. Careful bacteriological study of a sample of this spinal fluid done at the Mulford Laboratories was completely negative. It was obvious that a marked change for the worse had taken place in the course of one hour previous to the serum injection. The patient had become deeply stuporous and completely disoriented. At 1:20 a.m. a severe chill occurred which lasted 25 minutes. Sulfanilamide, gr. xxx, was given by mouth followed by gr. xv every four hours. This was discontinued at the end of 36 hours because of the lack of any beneficial effect. Phenobarbital was also given for the control of restlessness.

On April 26, at 12:30 p.m., the clinical picture was that of a deep coma with increased rigidity of the neck, definite ankle clonus, knee jerks which varied in their response, coarse tremors of the face and extremities and cyanosis of lips and nails. Temperature was 104.2° F., pulse 130, respirations 40. Blood pressure was 150 mm. of mercury systolic and 80 mm. diastolic. A spinal tap was repeated. The fluid was distinctly turbid and dropped out slowly. Its cell count was 1899. Globulin was increased. Sugar (Folin) was 95 mg. per cent, chlorides were 692 mg. per cent. Sixty-five c.c. of spinal fluid were removed, and 50 c.c. of immune serum were injected in the spinal canal. Following the tap, 450 c.c. of the serum were given intravenously by gravity. During the injection the patient perspired profusely and exhibited signs of fleeting paresis of the left side of the face. Throughout the day there occurred paroxysms of fine clonic contractions of the right hand and forearm with tremors of the left hand on motion. There was urinary incontinence. A specimen of urine revealed the presence of a faint trace of albumin and an occasional white blood cell. The blood count showed hemoglobin 75 per cent, red blood cell count 4,360,000, white blood cell count 15,450, polymorphonuclears 96 per cent, lymphocytes 4 per cent.

On April 27, at 9 a.m., the patient was definitely more rigid and stuporous and could not be aroused. The left hand showed ulnar deviation with the thumb and

* Supplied by Lederle Laboratories, Inc., through the courtesy of Mr. S. D. Beard.

forefinger pressed together. The Kernig sign was more marked on the right. No ankle clonus. A spinal tap was done. Spinal pressure was 10 mm. of mercury. Negative Queckenstedt sign. The fluid was less cloudy, but after standing a large number of flecks were seen on stirring. About 15 c.c. of fluid were removed and the pressure dropped to 2 mm. of mercury. Its cell count was 850. Polymorphonuclears 75 per cent, lymphocytes 25 per cent. Smear and culture were negative. After the tap was done, 350 c.c. of immune serum were given intravenously. There was no reaction but a chill which lasted 35 minutes. That night the patient was still in deep stupor but appeared to be less rigid. Coarse tremors of the left hand were present. At midnight the patient became conscious and talked rationally. The temperature was 101.3° F., pulse 130, respirations 32. Laboratory studies reported the blood sugar as 90 mg. per cent, the blood chloride as 432 mg. per cent of whole blood, and the blood urea as 15 mg. per cent.

On the following morning the patient was definitely improved. The rigidity of the neck was lessened and the upper extremities which had been stiff showed a normal tone. The Kernig sign was negative on the left and only suggestively positive on the right. The deep reflexes were normal and the patient was able to protrude the tongue. Fifty c.c. of immune serum were given intramuscularly at 9 a.m. Due to a sudden jerk, the needle broke at the hub. A hurried search was conducted, but the missing part remained buried in the left thigh. Another 50 c.c. of serum were injected at 9:45 p.m. The patient was better, responded to painful stimuli, and actually recognized the visiting physicians. Because of the profuse sweating, sodium chloride grs. v four times a day was prescribed. Temperature was 100.4° F., pulse 120, and respirations 34.

On April 29, at 11:30 a.m., the patient's sensorium was clear. He was oriented as to place and events and recognized his family. Upon request he attempted to smile. The neck was still stiff and the spine appeared to be more sensitive to pain. A spinal tap revealed a clear fluid (a few flecks were seen on stirring) with a cell count of 276. Globulin was normal. About 35 c.c. of fluid were removed. Forty-five c.c. of antiserum were then injected intramuscularly. Control of bowels and bladder had returned. At 9 p.m. the patient's facial expression was more relaxed. He occasionally smiled and expressed interest in the place of work. Breathing was quiet and regular in contrast to the previous night, when it was labored. The Kernig sign was negative. Temperature was 101.3° F., pulse 120, respirations 22. The red blood cell count was 4,290,000, hemoglobin was 75 per cent, white blood cell count 15,850, polymorphonuclears 92 per cent, lymphocytes 8 per cent.

On April 30, the patient showed steady improvement both mentally and neurologically. He asked for the newspapers and for a smoke. He understood and answered questions clearly. He complained of pain along both sternomastoid muscles, left shoulder and thigh, made worse by motion. The postcervical and inguinal nodes were palpable and slightly tender (serum sickness?). Perspiration was decreasing. The neck and spine showed decreased spasticity. The rest of the musculature showed normal tone. The biceps reflexes were exaggerated but equal. The triceps reflex was normal. The abdominal and cremasteric reflexes were absent. The knee jerk was slightly increased, and there was a slightly positive Kernig sign on the right side. No ankle clonus. Babinski sign was negative. The temperature was 99.3° F., pulse 120, respirations 28.

Next day the patient became very drowsy and was awakened with a great deal of difficulty. It was difficult to make him understand even simple questions. Urinary incontinence developed during the night. There was no change in the neurological picture. Adenopathy was the same. A punctate erythema and a few hives appeared on the chest. A spinal tap was done at 12:15 p.m. Blood was encountered. However, the fourth specimen was clear. The fluid dropped out slowly, but there was

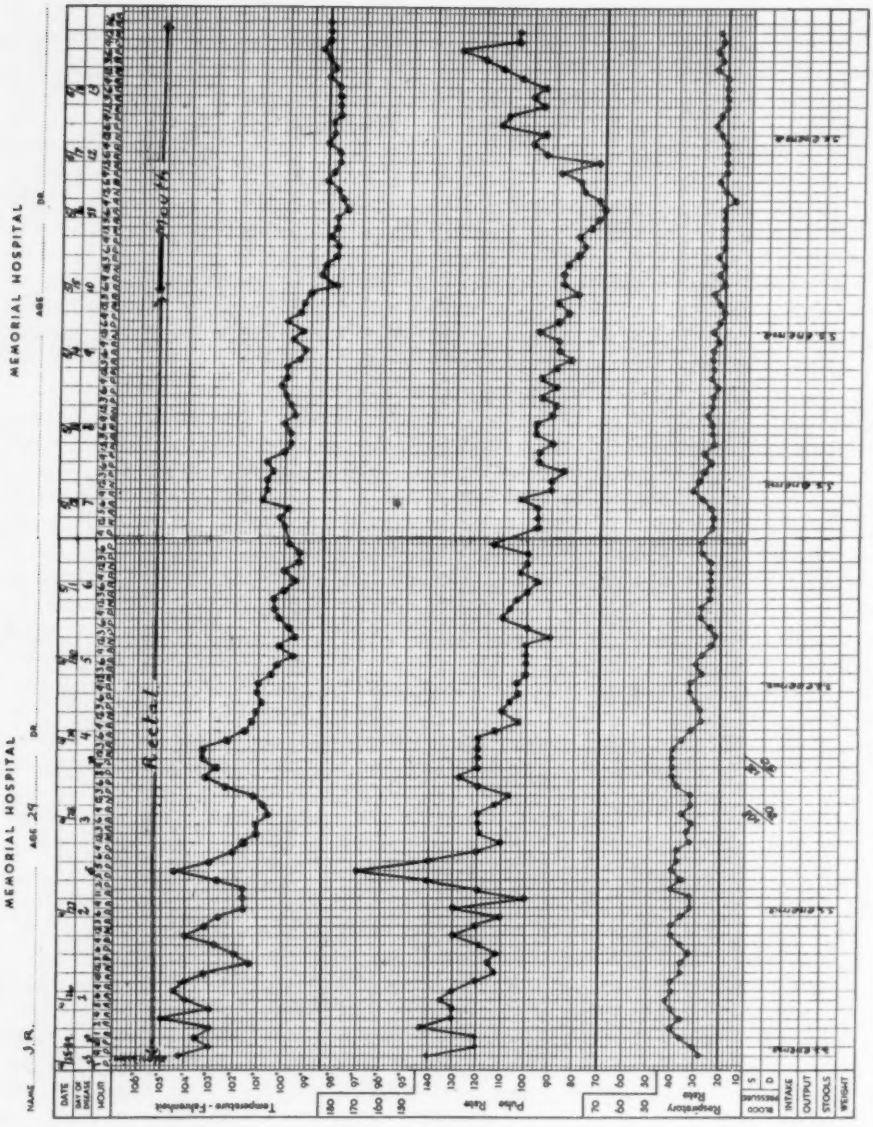
MEMORIAL HOSPITAL
NAME J. R.
AGE 29
DR.
MEMORIAL HOSPITAL
AGE
DR.
Temperature - Fahrenheit
Pulse Rate
Respiratory Rate
Admitted
Death
DATE
DAY OF DISEASE
HOUR
BLOOD PRESSURE
S
D
INTAKE
OUTPUT
STOOLS
WEIGHT

FIG. 1.

no block. Fifteen c.c. were removed. Fifty c.c. of 50 per cent sucrose were given intravenously and 2 c.c. of histaminase were injected intramuscularly in each thigh. The patient was seen again at 9:30 p.m. He had slept throughout the afternoon, drenched in sweat. He could now be aroused more easily but could not remain awake for more than a few minutes. The rash had disappeared from the chest but was present on the knees. The arms were painful. Muscle tone was normal. The neck was definitely less stiff. A coarse tremor of the tongue and hands was noted. Temperature was 100° F., pulse 104, respirations 24.

On May 2, the patient was alert and rational at noon, but when seen at 5:00 p.m. he could hardly be aroused. The erythema had disappeared, but a few hives came out throughout the day. Muscle tenderness was still present. Neck stiffness was unchanged. Kernig sign was positive on the left. A fine slow tremor of the eyelids and muscles around the mouth was noted. Two c.c. of histaminase were injected intramuscularly in each thigh. Temperature was 101.1° F., pulse 104, respirations 34. The blood Wassermann test was negative, the blood chloride was 464 mg. per cent of whole blood, and the blood urea was 13 mg. per cent. The urine was alkaline, specific gravity 1.050; it showed a faint trace of albumin, an occasional dark granular cast, an occasional epithelial cell, and a few white blood cells.

The patient was much improved when seen on May 3. He was wide awake and able to raise both arms. He grasped objects more easily and with lessened tremor of the hands. The neck was not as stiff and the knee jerks were less exaggerated. Profuse sweating was still present. An occasional hive and soreness of muscles of the left arm were noted. Temperature was 100° F., pulse 96, respirations 24. A spinal tap was done at 11:15 a.m. The pressure was 12 mm. of mercury. On compression of the jugular veins, it went up to 26 mm. but dropped promptly on release. The fluid was clear with no flecks or sediment. About 30 c.c. were drained. Final pressure was 2 mm. The cell count was 47, with 80–90 per cent lymphocytes. Globulin was negative. The red blood cell count was 4,160,000, hemoglobin 75 per cent, white blood cell count 15,850, polymorphonuclears 78 per cent, lymphocytes 22 per cent. Two c.c. of histaminase were injected in each thigh.

On May 4, the patient had a good day. He was able to keep awake and moved around in bed with ease. Facial expression was almost normal. Tremors of the lids, tongue, and left hand were still present. Abdominal reflexes were elicited for the first time. The only evidence of serum sickness was soreness in the left deltoid. Temperature was 99° F., pulse 84, respirations 24. Two c.c. of histaminase were injected in each thigh. Passive and active exercises were carried out to prevent atrophy which was quite noticeable.

We saw the patient again next day at 4:15 p.m., when he appeared improved. The neck could be bent to 15° short of its normal range. There were no signs of serum sickness. Temperature 98° F., pulse 80, respirations 20. At 6 p.m. the nurse noticed that the patient had become very listless and was staring into space. He seemed depressed and emotionally upset. He complained of frontal headache, and the pupils were widely dilated. Two c.c. of histaminase were injected in the muscles of the thigh, and 50 c.c. of 50 per cent sucrose were given intravenously for possible cerebral edema. The patient had a poor night.

When seen by us the next morning at 11 o'clock, the patient's appearance and mental reactions were decidedly worse. He was listless and had a vacant stare. There was a marked tremor of the lids, tongue, and muscles around the mouth. The patient did not talk readily and spoke in a very low tone. He refused food and stated that he had an ache above the eyes and that he had not slept well. There was profuse sweating. Both eyes showed conjunctival injection and swelling (serum sickness?). Neurological signs showed improvement except for the marked tremor of the head. A spinal tap was done. The fluid was clear (few flecks on stirring) and

FIG. 1.

under 6 mm. of mercury pressure about 10 c.c. were removed. Cell count was 31 with 90 per cent lymphocytes. Globulin was normal. Four c.c. of histaminase were given intramuscularly. Temperature 97.3° F., pulse 68, respirations 20.

On May 7, the nurse noted that the patient had difficulty in swallowing and breathing. He presented the picture of severe Parkinsonism with mutism. Temperature 98° F., pulse 96, respirations 20.

The next day, Dr. A. M. Ornsteen, of Philadelphia, saw the patient in consultation. His report read as follows:

"The general appearance of the patient is striking and at once diagnostic of the nature of the motor disability, i.e., extra-pyramidal akinesis or the pseudo-catatonic state of Parkinsonism. He lies immobile on his back and his eyes are fixed in the position of staring ahead. He does not turn his head in the direction of the speaker, but his intention to do so is indicated by the slow lateral associated movements of the eyeballs after it is insisted that he look in one direction or the other. The arms are in a semiflexed position with the hands resting on the body; the fingers are closely opposed to one another with the tip of the thumb opposed to the palmar surfaces of the index and middle fingers, the characteristic position of Parkinsonism, being more in evidence in the right hand than the left. The lower limbs are in extension and the patient is capable of moving the extremities but in a very slow manner, both the upper and lower limbs being markedly hypertonic, and on passive motion the increased tone is recognized as rigidity of the extra-pyramidal type; the upper limbs show the characteristic cogwheel type of hypertonus at the elbows and wrists.

"There are hyperkinetic features in the clinical picture and they are confined to the eyelids and tongue. The eyelids show a constant coarse tremor, the frequency of about three to five a second but fairly irregular. Occasionally there occurs blepharospasm with complete closure of the eyes, at the cessation of which the tremor is again in evidence. The eyes are moved laterally and upward in a normal fashion and with good associated innervation, but convergence is deficient. Pupils are dilated but equal and react to light and accommodation. Ophthalmoscopic examination discloses no pathological changes in the discs, vessels, or retinae. No nystagmus was noted. The wrinkling of the brow is slightly possible, closure of the lids is complete but not forceful, and retraction of the corners of the mouth is barely possible. The patient hardly opens the mouth and attempts to protrude the tongue but can bring only the tip of it beyond the dental line and it is coarsely tremulous. The mouth is full of stagnant thick saliva which fills the fauces, and the patient occasionally swallows with deliberate effort to down the excess fluid accumulated in his throat. Vital sensation is apparently preserved, but because of the patient's inability to speak gnostic sensibilities could not be tested. During this examination the patient was totally mute. The tendon reflexes at the elbows are elicited but not pathological; the patellar tendon reflexes are bilaterally hyperactive to the same degree, the Achilles jerks are equal and normal; the plantar reflexes are of the normal flexor type. The lower abdominal and cremasteric reflexes are absent; the upper abdominals were elicited quite normally. No tremor of the extremities was seen. There is marked resistance on passive flexion of the head and extension of the legs producing positive Kernig and rigid neck signs, but these are only apparent because the resistance is due to hypertonicity rather than reflex meningeal contraction.

"The present clinical picture is that of a severe and widespread mesencephalitis producing a very marked state of Parkinsonian akinesis associated with a hyperkinetic phenomenon affecting the eyelids and tongue as described above; the mutism is part of the state of akinesis. Because of the latter symptom it is difficult to examine the psychical reactions of the patient, but he impresses me as being mentally clear, since he showed fairly good apperception and attention and coöperation as far as it was possible. I envisage a pathological involvement of both lenticular nuclei,

especially the globus pallidus segment, the substantia nigra and possibly the red nuclei because of the constant slow tic-like tremor of the eyelids apart from the intermittent blepharospasm. The development of the basal ganglia symptom-complex in the third week of the disease, at a time when all indications of the infectious process had subsided, indicates pathological injury of the aforementioned structures by perivascular cellular infiltration and ganglion cell degeneration.

"When acute Parkinsonism develops in the course of epidemic encephalitis the disability is permanent, and I see no reason to believe otherwise in this case of equine encephalomyelitis virus. However, it is possible for improvement to take place with disappearance of edema so that the patient may become ambulant. If this is going to take place, there should be indications of clinical improvement within the next three to six weeks. Amphetamine sulphate may be tried empirically at the present time in an effort to stimulate the psyche into some degree of spontaneity, 5 mg. three times a day and gradually increased according to the effects."

May 9. Temperature 98.4° F., pulse 112, respirations 24. Patient shows marked weakness. A large amount of mucus was aspirated from the throat. Dr. Ornsteen's therapeutic suggestions put into effect.

May 10. Some hives appeared on the extremities. Conjunctivae are injected. When addressed the patient is able to interrupt his vacant stare for a few minutes. Now able to expectorate. Two c.c. of histaminase were given intramuscularly in each thigh. Amphetamine sulphate, 5 mg., given three times a day.

May 11. There is no change in the clinical picture except that the tremor of the lids is not as marked. Patient sits up to carry out muscular exercises. Urticaria is so pronounced that four doses of epinephrine hydrochloride were required for relief. Four c.c. of histaminase were given intramuscularly. Fluid intake good. Temperature 99° F., pulse 120, respiration 20.

May 12. Body is still covered with hives. Epinephrine hydrochloride was given subcutaneously and in the eyes. Patient is able to sit up in bed without support. No change in the muscular rigidity or mutism. Fifty c.c. of 50 per cent sucrose were given intravenously. Four c.c. of histaminase were injected intramuscularly.

May 13. Patient is more alert today. He smiles occasionally, reads the newspaper and moves around in bed with greater ease, but can't open his mouth and can't chew. Perspires a great deal. Hives still present. Two c.c. of histaminase given. One ounce of vitamin B complex taken by mouth; 50 c.c. of 50 per cent sucrose given by vein.

May 15. Temperature has remained normal. Patient is much improved. Slow blinking, occasional blepharospasm and staring still present. Able to open the mouth a bit wider, but can't protrude the tongue. The chin and lips quiver and tremble on effort. Began to talk yesterday morning. Utters single words. Muscle and neck rigidity are decreased and movements of the hands are more regular. Negative Kernig sign. No hives. Hemoglobin 75 per cent, red blood cell count 4,222,000, white blood cell count 10,350, polymorphonuclears 62 per cent, lymphocytes 38 per cent.

May 17. Patient shows decided improvement. His speech is clear. He does not stare as much and laughs a great deal. Winking, though present, is pronounced only after excitement. Able to open the mouth fully and to protrude the tongue. Right eye shows deficient convergence. Muscle tone is returning to normal. Coordination improved. Patient tried to stand on scales, but felt too weak.

May 18. Out of bed for ½–1 hour. Tired easily. Only medication given is Amphetamine sulphate (gr. ½ t.i.d.) and Vitamin B complex, one ounce daily.

May 19. Speech shows marked improvement. Powers of concentration excellent. Playing cards with the nurse. High caloric intake.

May 20. Patient brushed his own teeth and fed himself. Walks around the room with ease and gait is grossly normal. Muscle tone normal. Neurological ex-

amination negative, except for occasional tremors of lids, tongue, and lips. Amphetanine sulphate by mouth was discontinued.

May 21. Walking alone for considerable distance. Tremor of lids is more pronounced when tired.

May 23. Needle removed by Dr. T. J. Fleming under local anesthesia and fluoroscopic control. Excitement has made tremor more intense. Preoperative urine examination was negative.

May 26. Walking well. Tremor of lids still present. It is of slow type and especially noticeable on closing of lids. Tremor of tongue lessened.

May 30. Patient feels very well after a long walk. Appetite good. Gaining weight. Muscle power and tone normal. Good performance of fine motions. Memory of present events is good. Patient does not remember anything that transpired during the first 12 days after admission to the hospital. Four capsules of Vitamin B complex given daily.

June 2. Patient is very active. He still has slight tremors of the lids. Good muscle control except over the left foot, which he stamps down on walking.

June 3. Discharged from the hospital. Seen by Dr. Ornsteen at his office for neurological check up. Results of examination were as follows:

"Neurological reëxamination today discloses the very startling fact that the acute striatal status of complete akinesia and segmental tremor has disappeared! The patient appears to be as normal in the motor sense as one can expect except for a slight dysergia in the use of the left lower limb in walking which the patient is aware of in the form of a little heaviness of that limb when tired, and the left arm does not swing as much as the right, but it is not motionless. The muscle tone is normal in all four limbs and there is not the slightest suggestion of the cogwheel type of rigidity. The extended hands show no tremor of the finger tips, but the eyelids flutter abnormally when he shuts his eyes and the previously continuous twitching of the lids is not present today. There is no obvious tremor of the facial muscles or tongue except when he firmly innervates these muscles by retracting the corners of the mouth and protrudes the tongue when one sees a little exhaustability of innervation and a fine tremor which is not constant.

"The relative posture of the finger tips to the thumb is normal on each side, the finger spacing of the outstretched hands is symmetrical and the repeated thumb and forefinger apposition movement (diadokokinesia) is of normal amplitude in each hand. The pupils are quite wide in dilatation but symmetrical and react promptly to light and accommodation. The extra-ocular movements are full without nystagmus and convergence is done well. The eyegrounds are negative. Facial innervation is symmetrical and there is no bulbar weakness. The left biceps and triceps reflexes are more active than the right, the difference between the biceps being more marked than between the triceps. There is no Tromner reflex in either hand. The knee jerks are markedly exaggerated to the same degree, while the Achilles reflexes are moderately hyperactive but without clonus. The plantar and abdominal reflexes are normal, the latter markedly hyperactive; neither cremasteric reflex could be elicited. All forms of vital and gnostic sensations were tested and found intact throughout. The patient's speech is clearly enunciated, and there is not the slightest suggestion of dysrhythmia of articulation. He impresses me as being mentally alert, and there is nothing to suggest any deviation from the normal in the intellectual sphere.

"It would now appear that the acute striatal disturbance which was observed in the early part of May was due to perivascular edema rather than hemorrhage or an infiltrative tissue process, otherwise the disturbance would not have cleared up so completely in the short space of two weeks. The clinical course is a sound basis for a good prognosis, but one must make this with a certain reservation, namely, that there

is a possibility of the insidious development of Parkinsonism in the next year or two if only based on the experience with acute epidemic encephalitis."

Immunological Studies

(*a*) *Isolation of Virus.* Efforts were made to recover the virus from both the spinal fluid and blood serum drawn after admission to the hospital prior to the administration of antiserum. Chick embryos and mice were injected with each fluid. Five 12-day chick embryos were each inoculated with 0.1 c.c. of blood serum and five with 0.1 c.c. of spinal fluid; three were inoculated with 0.5 c.c. each of blood serum and three with 0.5 c.c. each of spinal fluid. From a total of 16 embryos thus injected, one died. This embryo, which had received 0.1 c.c. of blood serum, died in less than 24 hours, and although no lesions characteristic of encephalomyelitis were apparent, the dead chick was ground finely with alundum, the ground tissue then diluted with broth to 10 per cent suspension, and the supernatant fluid transferred to other embryos and mice. The embryos remained healthy and were discarded after a week. The mice were held for three weeks; no symptoms of encephalomyelitis were shown at any time.

Both the blood serum and the spinal fluid were each injected intracerebrally (0.03 c.c.) into five 21-day old Swiss mice. The mice were observed daily; no symptoms of encephalomyelitis developed. At the end of six weeks the animals were tested for susceptibility to the virus by injecting them intracerebrally with a dose of virus estimated as one lethal dose. In both sets of animals three out of five mice promptly developed encephalomyelitis and died at the same time as the controls. There was, therefore, no evidence that the animals had developed an immunity due to a subclinical infection.

(*b*) *Tests for Antiviral Neutralizing Antibodies.* Specimens of blood serum and spinal fluid taken at various times during the patient's illness and period of recovery were studied for their antibody content. The specimens were kept frozen at — 20° C. and were tested at one time. The tests were made according to the intracerebral method of Cox and Olitsky.[6] Mixtures of equal volumes of blood serum or spinal fluid and virus dilutions were allowed to stand at 37° C. for 45 minutes, after which they were injected intracerebrally (0.03 c.c.) into 21-day old Swiss mice. The description of the specimens tested and the results obtained are given in table 1. These tests were repeated three times with essentially the same results. In two tests, chick embryo propagated virus was used as a source of virus; in the third test, mouse brain passage was employed.

It is apparent that neither the spinal fluid nor the blood serum taken before the administration of antiencephalomyelitis serum contained definitely demonstrable antibodies. The results obtained with the blood serum suggest a trace of protection against one to 10 lethal doses of the virus, but in no one of the three tests made was the protection clear-cut. After the administration of very large doses of antiserum, both intravenously and intrathecally, antiviral immune substances were easily demonstrated in both blood serum and spinal fluid. This rise in antibody content can be entirely accounted for by the high potency of the antiserum employed. Tests showed that 0.015 c.c. of the antiserum neutralized 10,000 intracerebral mouse doses. It is interesting to note that the antibodies present in the spinal fluid as the result of the intraspinal and possibly the intravenous administration of antiserum disappeared within seven days.

TABLE I

Results of Tests for Neutralizing Antibodies to Encephalomyelitis Virus (Western Type) Iowa 1937 Strain, in Specimens of Spinal Fluid and Blood Serum. Chick Embryo Passage No. 4 Used as Source of Virus. Five Mice Injected Intracerebrally with 0.03 c.c. of Each Mixture

Specimen	Date Obtained	Virus Dilutions								M.L.D's Protected Against
		10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	
Spinal fluid No. 1 (specimen before antiserum)	4-26-39				3,*4,5,5,5	4,5,5,6,6	4,4,5,6,6	5,S,†S,S,S	S,S,S,S,S	1 (?)
Spinal fluid No. 2 (immediately after 550 c.c antiserum were injected intravenously)	4-26-39				5,5,5,5,6	5,6,6,6,8	4,5,6,6,S	5,S,S,S,S	S,S,S,S,S	1 (?)
Spinal fluid No. 3 (12 hrs. after 550 c.c. and 50 c.c. of antiserum were injected intravenously and intraspinally respectively)	4-26-39				4,5,5,6,7	6,7,8,S,S	Tr‡,Tr,S, S,S	S,S,S,	S,S,S,S,S	10–100
Spinal fluid No. 4 (24 hrs. after second intraspinal (50 c.c.) and intravenous (450 c.c.) injections of antiserum)	4-27-39				Tr,4,4,5,5	3,5,5,6,S	4,S,S,S,S	S,S,S,S,S	S,S,S,S,S	10
Spinal fluid No. 5 (after additional injections of antiserum 4-27-39—350 c.c. intravenously; 4-28-39—100 c.c. intramusc.; 4-29-39—50 c.c. intramusc.	5- 1-39				4,5,6,6,8	3,5,5,5,5,S	4,4,S,S,S	5,S,S,S,S	S,S,S,S,S	10
Spinal fluid No. 6	5- 3-39				3,3,4,4,4	3,4,5,5,6	5,5,9,S,S	S,S,S,S,S	S,S,S,S,S	1
Standard antiserum control (western type)			5,6,8, S,S	S,S,S S,S	S,S,S,S,S	S,S,S,S,S				10,000
Virus controls (broth)					3,4,3,5,5	3,5,5,6,6	3,3,6,6,6	6,6,9,S,S	6,S,S,S,S	
Blood serum No. 1 (specimen before antiserum)	4-26-39				4,4,6,7,7	3,4,5,5,7	3,5,5,6,6	4,6,6,S,S		1–10 (?)
Blood serum No. 2 (immediately after antiserum). See spinal fluid No. 2	4-26-39				4,5,5,7,7	5,6,7,S,S	S,S,S,S,S	S,S,S,S,S		100+
Blood serum No. 3 (see spinal fluids No. 3 and No. 4)	4-27-39			5,6,7, 7,9	4,4,4,4,5	5,5,5,S,S	S,S,S,S,S	S,S,S,S,S		100+
Blood serum No. 4 (4 mos. after onset of disease)	8-23-39	S,S,S, S,S	S,S,S, S,S	6,S,S, S,S	S,S,S,S,S	8,S,S,S,S	7,S,S,S,S	S,S,S,S,S		10,000,000+
Standard antiserum control (western type)		5,8,9, 11,S	6,7,7, 7,7	5,5,5, 5,9	8,S,S,S,S	5,S,S,S,S				10,000
Virus controls (broth)					3,3,4,4,4	3,3,4,4,4	3,4,4,5,7	4,4,5,5,10	4,5,7,S,S	

* Figures indicate day of death of each mouse. † S indicates survival for ten days. ‡ Tr indicates death from trauma.

After recovery and four months after onset of illness, 0.015 c.c. of the patient's blood serum neutralized at least a million lethal doses of the virus. The demonstration of this high titer after recovery in contrast to the questionable presence of antibodies at the onset of the disease offers sufficient evidence as to its etiology in spite of our failure to recover the virus from the spinal fluid or blood. A specimen of blood drawn eight months after the onset of the disease (December 12, 1939) also protected mice against 1,000,000 lethal doses of virus. A specimen of blood taken four months later (April 24, 1940) still contained neutralizing antibodies. Though its titer had dropped, it protected mice against 10,000 lethal doses of virus.

Tests made on two specimens of blood serum taken after recovery failed to protect against a single lethal dose of the Eastern type of virus.

Follow-Up

The patient returned to work on July 5, 1939, when he was assigned to a different department. He was seen by one of us (H. G.) on July 16, 1939, when he had regained his normal weight (127 lbs.). Appearance was normal. No staring. There was a slow steady tremor of the lids. There was also a coarse tremor of the tongue on extension. Gait was normal except that the left arm did not swing as much as the right. There was no difficulty in walking except that, when tired, the patient was forced to stamp the left foot. Otherwise it was normal. The deep reflexes were prompt and equal. Abdominal reflexes were normal. Could not elicit the cremasteric reflexes. Patient stated that in the last two weeks he noted a diffuse loss of hair. Still taking Vitamin B complex capsules (4 a day).

He was examined again on May 25, 1940. Weight was 127½ lbs. There were no complaints. Memory and powers of concentration were good. The sensation of stamping of the left foot had disappeared. Played golf well, without undue fatigue. Hair growth was normal. Frequent winking was noted. On closing the lids a fine regular tremor occurred (the patient was not conscious of the winking although his girl friend had drawn his attention to it and asked him to stop it). Pupils were in mid-position, equal and reacted to light and accommodation. There was a coarse tremor on extreme protrusion of the tongue. The patient smiled well and the expression was normal, but on forced contraction of the mouth there was noted some quivering of the muscles of the chin and lower lip. The biceps reflexes were more active on the right, the triceps were normal, and the knee jerks were hyperactive, but equal. Upper abdominal reflexes were exaggerated while the left lower abdominal and cremasteric reflexes were absent. Muscle tone was normal throughout the body. Romberg and Babinski tests were negative. Finger to nose test and apposition movements were normal although he tired rather easily. There was a slight tremor of the left hand. Gait was normal. Libido was normal.

A final neurological reëxamination was done by Dr. A. M. Ornsteen on July 31, 1940, who reported the following:

"The mild reflex changes and leftsided associated movement defect found a year ago have entirely disappeared. The station and gait are normal; both arms move actively in their normal associated movements with the lower limbs. His station is secure in the Romberg position; there is no fluttering of the eyelids; his extended hands show no tremor of the finger tips; and he performs the finger-to-nose test equally well on the two sides.

"There is a tendency for the left pupil to be slightly larger than the right in a subdued light, but the difference is not noticeable in a well-lighted room. Both pupils react promptly to light and accommodation. The extra-ocular movements are full

without nystagmus and the eyegrounds are normal. Facial innervation is full and symmetrical; the tongue protrudes in the mid-line without tremor; and the retracted corners of the mouth remain equally retracted without fatigability on either side or tremor of the perioral muscles. The soft palate is normally innervated; facial sensation is normal and the corneal reflexes are active.

"The tone of the musculature of the upper and lower limbs is normal and equal on the two sides of the body, there not being the slightest suggestion of extrapyramidal cogwheel tension in the left upper limb, the extremity which was originally predominantly involved. The posture of the fingers is normal and he executes perfectly rapid alternating movements with the fingers of each hand. The tendon reflexes at the elbows are bilaterally hyperactive in a moderate degree but equally so; there is no Tromner reflex in either hand. The knee and ankle jerks are quite hyperactive but to the same degree in each limb. The abdominal reflexes are exceedingly hyperactive, both the upper and lower; the cremasteric reflexes could barely be obtained; both plantar reflexes are of the normal flexor type. All forms of vital and gnostic sensation were found intact throughout. The patient is mentally alert and his speech is normal.

"Subjectively J. R. is perfectly normal and says that the occasional headache he has is no more than he had prior to his serious illness of last year. He has had no recurrence of any of the cerebral symptoms which complicated his acute ailment. It can be safely stated that he has no residual signs of his former organic brain disease and there is nothing to suggest a beginning late extra-pyamidal symptom-complex such as often complicates epidemic encephalitis. Last year I reported a moderate hyperactivity of the leftsided reflexes as compared to the right; this is not in evidence today. The absent cremasteric reflexes at that time were associated with hyperactive abdominal reflexes, and the same is noted today. I do not consider this of importance. The fine tremor of the lips and the fluttering of the closed eyelids reported then are absent today."

Summary

The clinical record and follow-up observations of a laboratory infection with encephalomyelitis virus (Western type) are here presented. Although the virus was not recovered from the patient's blood or spinal fluid, the appearance in the blood of specific neutralizing antibodies in extremely high titer after recovery (when passive immunity is out of the question) in contrast to the doubtful presence of immune substances at the onset of the disease constitutes convincing laboratory proof of the etiological agent involved. Large quantities of a highly potent immune horse serum were administered intravenously and intrathecally. Acute Parkinsonism developed at the end of the second week of the disease when signs of infection had subsided. At that time the patient was suffering from serum sickness. Complete recovery occurred.

Addendum

Since this report was submitted for publication Zichis and Shaughnessy (Jr. Am. Med. Assoc., 1940, cxv, 107) have presented interesting experimental evidence concerning the therapeutic value of large doses of highly potent immune rabbit serum in the treatment of experimentally induced Western equine encephalomyelitis in guinea pigs and mice. This is in line with the clinical impression obtained from our case.

We wish to thank Drs. LeRoy Wenger, H. B. Conaway, S. F. Gilpin, and A. M. Ornsteen of Philadelphia for the clinical notes they made on this case.

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NON-ICTERIC LEPTOSPIROSIS ICTEROHEMORRHAGIA (WEIL'S DISEASE) CONTRACTED WHILE BATHING*

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BECAUSE the term Weil's disease is usually associated with a severe infection with jaundice and bleeding, it is possible that the correct diagnosis of cases without these features is seldom made. According to several opinions jaundice is said to be present in about 50 per cent of cases, but it is probable that if all mild cases were recognized the proportion would be much lower. Jaundice and bleeding are characteristic of the severe infections. Since a clinical diagnosis can not be made in the mild form, it is necessary to apply various biologic tests. It is important, of course, that the mild as well as severe cases be recognized.

Studies elsewhere in the world, especially in Europe and in the East Indies, show that numerous other varieties of leptospira may cause infection similar to Weil's disease in which jaundice is reported in less than 5 per cent of cases. The subject was recently reviewed by Havens, Bucher and Reimann.[1]

Infection with leptospiras during bathing or submersion in water contaminated with the excreta of rats, the common source of the disease, has long been recognized, but only recently have out-breaks been recorded in this country.[1] The following report describes a case contracted in this manner.

CASE REPORT

On September 3, 1938, a man, aged 25, swam in a quarry pond. Rats were seen running about the adjacent rocks. Nine days later he was taken with severe cramps in the abdomen, diarrhea, intense headache, pains in the back and legs, and fever of

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103.4° F. The pulse rate was 126 per minute, the blood pressure 90 millimeters of mercury systolic and 60 diastolic. The conjunctivae soon became deeply injected and a subconjunctival hemorrhage appeared in the left eye. There was no jaundice. The pharynx appeared to be deep red and plush-like, the liver and spleen became enlarged and tender, and the cecum was distended. Peristalsis was greatly increased and signs of meningismus developed.

The erythrocytes on the third day of the disease numbered 3,700,000 per cubic millimeter of blood, the leukocytes 15,000, of which 59 per cent were polymorphonuclear cells, 24 per cent lymphocytes, 8 per cent monocytes, 7 per cent eosinophile cells and 2 per cent basophiles. The hemoglobin measured 60 per cent (Sahli). The urine contained albumin and erythrocytes; the specific gravity was 1.035. Agglutinins for *Leptospira icterohemorrhagiae* were absent during the disease. The icterus index was 7 and 8 units on two occasions. Dark field study of both blood and urine at intervals failed to reveal leptospiras. On the fourth day of the disease five cubic centimeters of the patient's blood were injected intraperitoneally into each of two guinea pigs. On the eighth day five cubic centimeters of the patient's urine were injected intraperitoneally into two more guinea pigs. The first two animals died seven and eight days after inoculation, the latter two died 10 and 12 days after inoculation respectively. All four guinea pigs were studied post mortem. There was general icterus of the tissues; and there were hemorrhages in the lungs, intestines and kidneys. Leptospiras were found in the liver on microscopic examination. Samples of water were then obtained from the pond in which the patient swam; one gallon was taken from the edge and one gallon from the middle of the pond. These specimens were concentrated by centrifugation and the sediment injected intraperitoneally into guinea pigs. No evidence of infection appeared.

The patient was given daily intravenous injections of 200 c.c. of 10 per cent solution of glucose. Codeine sulfate was used liberally to relieve pain. The fever gradually returned to a normal level after eight days, only to rise suddenly to 38.9° C. (102° F.) three days later. The fever continued for another five days when it began to fall; it reached normal after four days. Asthenia persisted for two months.

Summary

A man aged 25 contracted non-icteric leptospirosis while bathing in water polluted by rats. It is of importance to bear in mind the danger of infection with these microörganisms when bathing in quiet water likely to be contaminated with the excreta of these rodents.

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VENTRICULAR FIBRILLATION IN ACUTE CORONARY ARTERY THROMBOSIS DURING THE INTRAVENOUS ADMINISTRATION OF QUINIDINE SULPHATE; REPORT OF A FATAL CASE*

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INTRODUCTION

THE ectopic rhythms which occur following an acute myocardial infarction are usually transitory and benign. Sometimes ventricular tachycardia is an exception to this rule. This arrhythmia has been produced experimentally by ligation of the coronary arteries, and Levine [1] observed it frequently in acute myocardial infarction. Master,[2] on the other hand, found that it occurred in coronary occlusion infrequently except following the use of digitalis. The ischemic area is hyperirritable and a source of this idioventricular rhythm. Epinephrine enhances this irritability not only by increasing the myocardial ischemia at a time when a greater blood supply is needed,[3] but also because its direct toxic effect further accentuates the excitability of the myocardium. Wiggers [4] believes that the use of this stimulating drug cannot be expected to benefit an anoxic mammalian heart and that it usually sets up multiple ventricular pace makers. Further, anything that depresses the normal regulatory function of the Tawara-His Purkinje system on the ventricular myocardium, as quinidine, may precipitate this rhythm. Smith et al.[5] proved experimentally in dogs that after the intravenous administration of quinidine sulphate and subsequent coronary artery ligation the myocardium is more sensitive to the establishment of ectopic foci, and conclude that this drug is of little use in the preventive treatment of ventricular tachycardia or ventricular fibrillation.

It is highly probable that the administration of adrenalin brought about ventricular tachycardia in the following case, and that the subsequent use of quinidine led to ventricular fibrillation and death.

CASE REPORT

M. M., a robust 57-year-old white male, had been free from any evidence of heart disease until 36 hours before admission to the Kingston Hospital on the afternoon of July 20, 1940. At that time, while performing an unusually arduous task, he was suddenly seized with a severe crushing pain in the interscapular area radiating anteriorly to the epigastrium, accompanied by nausea, vomiting and, later, slight dyspnea. Dr. H. Keator of Kingston, New York, instituted the usual therapeutic procedures for acute coronary occlusion, but because of persistent vomiting, glycosuria and acetonuria, hospitalization was advised. Shortly after admission to the hospital, the patient was in no great distress but complained of nausea and dull pain in the interscapular area radiating anteriorly to the sternum and down both arms. Dyspnea was not marked, but there was slight cyanosis. Upon examining the fundi, slight arteriosclerotic changes in the retinal arteries were noted, but there were no hemorrhagic or atrophic areas. The blood pressure was 98 mm. Hg systolic and 64–60 mm. diastolic, and the pulse was regular with a rate of 94. A localized pericardial friction rub of mild intensity was heard over the left sternal border, and the heart sounds had an

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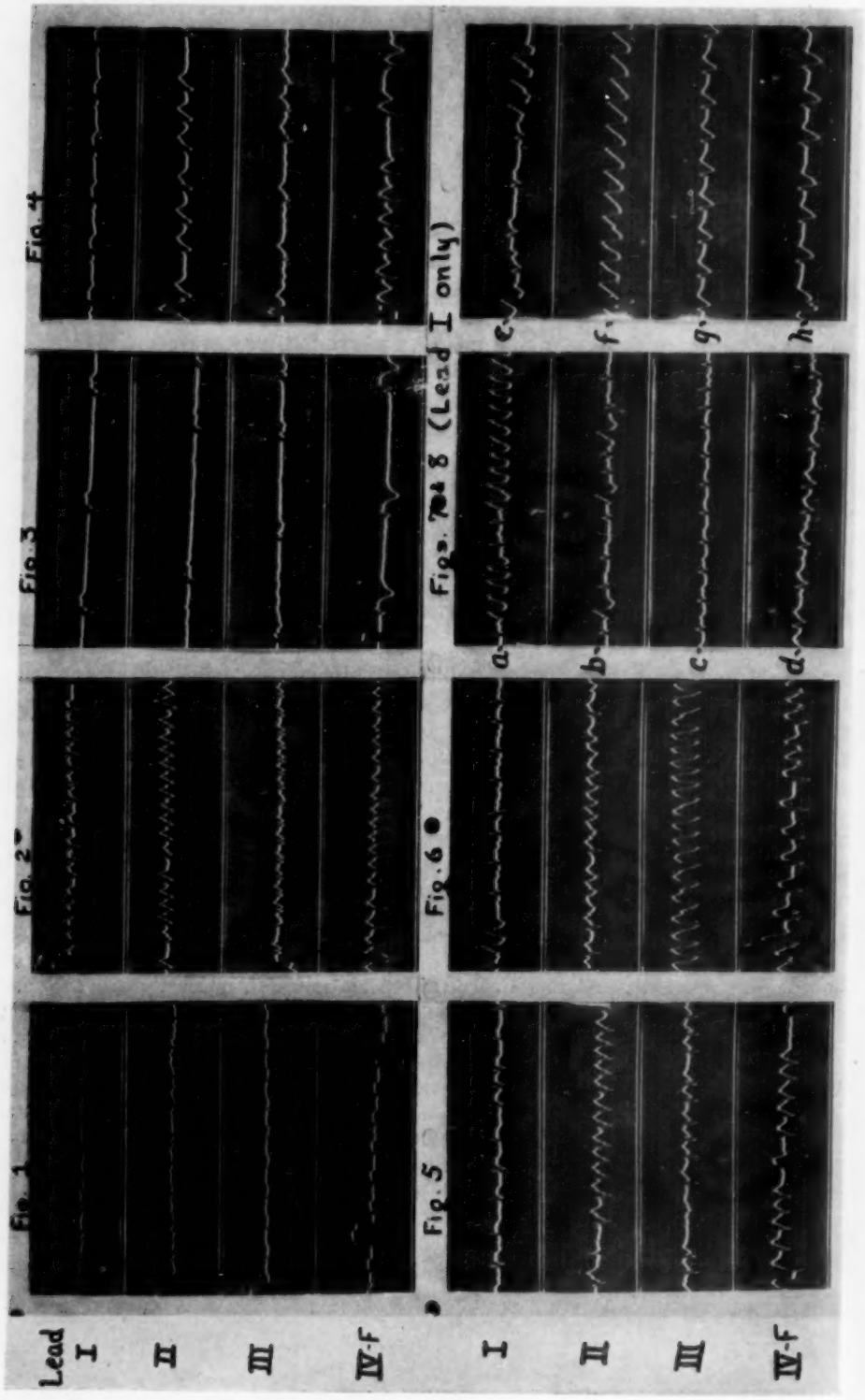
Lead
I
II
III
IV-F
Fig. 1
Fig. 2
Fig. 3
Fig. 4
Fig. 5
Fig. 6
Figs. 7 & 8 (Lead I only)
a
b
c
d
e
f
g
h

embryocardial quality. A few crepitant râles were heard at the base of the right lung, but there was no enlargement of the liver, nor was there peripheral edema. The electrocardiogram (figure 1) revealed normal sinus rhythm with evidence of a recent myocardial infarct of the anterior pattern. Chemical analysis of the urine showed marked glycosuria and acetonuria, but the microscopic examination was essentially negative. Blood studies revealed 275 mg. of sugar per 100 c.c. of blood, a carbon dioxide combining power of 54 volumes per cent, 5,950,000 erythrocytes per cu. mm., with 108 per cent of hemoglobin (15.6 gm. = 100 per cent), and 22,100 leukocytes per cu. mm., 88 per cent of which were polymorphonuclears. Subsequent determinations of blood sugar and carbon dioxide combining power varied only slightly from the above.

It was concluded that we were dealing with an acute myocardial infarct in an individual with previous asymptomatic diffuse vascular disease involving the coronary arteries. The glycosuria and hyperglycemia often observed in coronary thrombosis were doubtless due in part to the diffuse vascular disease and in part to a compensatory physiological response of the body. The acetonuria was probably caused by persistent vomiting with dehydration and was not accompanied by ketosis. Fluids were given parenterally, but insulin was not indicated.

Under the usual régime of bed rest, morphine and oxygen, the patient was quite comfortable until the next morning when, because of slight increase in dyspnea, unaccompanied by any change in the character of the pulse, an intern gave 15 minims of adrenalin. Shortly thereafter the patient became semicomatose and Cheyne-Stokes respirations, nausea, vomiting and cyanosis, together with a precipitous drop in blood pressure, were noted. The heart beat at the apex was rapid, slightly irregular, and the varying intensity of sounds suggested paroxysmal ventricular tachycardia. This was confirmed by electrocardiographic studies (figure 2).

Seven grains of quinidine sulphate in 70 c.c. of normal saline (as advised by Hepburn and Rykert[6]) were then given intravenously over a period of 35 minutes, when a classical Stokes-Adams syndrome ensued and an electrocardiogram revealed complete A–V dissociation (figure 3). However, within 10 minutes normal sinus rhythm was established followed by frequent interpolations of ventricular extrasystoles (figure 4). Concomitantly, the patient roused from his comatose state, cyanosis disappeared, respirations became easier, and the blood pressure rose. On the following day, because of persistent premature ventricular beats (figure 5), a total of 20 grains of quinidine sulphate was administered orally in divided doses over a period of 16 hours. The patient against became semi-moribund, cyanotic and dyspneic, and the electrocardiogram (figure 6) revealed rather prolonged and frequent paroxysms of

FIG. 1. Electrocardiogram taken on admission at 1:00 p.m., July 20, 1940, showing evidence of acute myocardial infarction of anterior pattern, with normal sinus rhythm.

FIG. 2. Electrocardiogram, 10:30 a.m., July 21, 1940, following the administration of 1 c.c. adrenalin, showing ventricular tachycardia.

FIG. 3. Electrocardiogram, 11:05 a.m., July 21, 1940, following administration of seven grains of quinidine sulphate intravenously, showing complete auricular ventricular dissociation.

FIG. 4. Electrocardiogram 10 minutes after the discontinuance of intravenous quinidine as in figure 3, showing return to normal sinus rhythm followed by paroxysms of ventricular tachycardia.

FIG. 5. Electrocardiogram at 11:00 a.m., July 22, 1940, showing persistence of paroxysms of ventricular tachycardia.

FIG. 6. Electrocardiogram at 10:30 a.m., July 23 1940, still showing persistence of paroxysms of ventricular tachycardia in spite of oral quinidine therapy.

FIGS. 7 and 8. Series of electrocardiograms in Lead I, during the intravenous administration of five grains of quinidine sulphate, started at 11:25 a.m. and continued over a period of 30 minutes, showing a transition from ventricular tachycardia to ventricular fibrillation. *a*—11:30 a.m.; *b*—11:40 a.m.; *c*—11:45 a.m.; *d*—11:50 a.m.; *e*—11:52 a.m.; *f*—11:55 a.m. (quinidine discontinued); *g*—11:58 a.m.; *h*—12:03 p.m.

ventricular tachycardia. Intravenous quinidine was again resorted to, and over a period of 30 minutes 50 c.c. of the previously mentioned solution had been administered, when the patient gave a loud maniacal shriek, threw his arms and legs wildly about, attempted to jump out of bed and within 30 seconds collapsed. An almost continuous electrocardiogram in Lead I (figures 7 and 8) during this period of 30 minutes showed premature ventricular beats arising in multiple foci, paroxysms of ventricular tachycardia and, finally, ventricular fibrillation. After respirations had ceased and heart sounds became inaudible the electrocardiogram recorded actively for six minutes. Artificial respiration and the intravenous administration of coramine and caffeine sodium benzoate were of no avail, and finally adrenalin was given intracardially without benefit.

Discussion

It has been reported that ventricular tachycardia complicating acute coronary artery thrombosis can be abolished by the use of quinidine, and now it is universally believed that the drug may control this purposeless, inefficient rhythm. Quinidine will alleviate the symptoms of heart failure in such instances only in so far as it can slow the rate without diminishing the force of the heart beat. However, the drug, by its toxic action, may not only fail to slow the rate by restoring normal sinus rhythm but on the contrary may bring about ventricular fibrillation.

The favorable results reported by Hepburn and Rykert [6] with an average intravenous dose of 20 grains of quinidine have stimulated indiscriminate employment of this drug. But it is not clear how many of their series of nine cases were associated with recent myocardial infarction, and, strangely enough, their only immediate adverse, almost fatal result occurred with only nine grains of quinidine in an individual who developed ventricular tachycardia two weeks after an attack of coronary thrombosis.

Levine and Fulton,[1] in their series of eight cases of ventricular tachycardia following acute coronary thrombosis, noted a return to normal sinus rhythm following administration of either oral or intravenous quinidine. It is difficult to be certain what part the quinidine played in producing these results. It is worthy of note that six of the eight cases died within two weeks, a high mortality rate indeed for acute myocardial infarction. Apparently the basic disease process which ultimately decides the outcome in myocardial infarction can be adversely influenced by quinidine. The ectopic rhythms associated with acute myocardial infarctions are usually transient and generally revert to normal sinus rhythm with no specific medication.

Stopping this so-called circus movement is dependent upon the predominant ability of quinidine to shorten the responsive gap by prolonging the refractory period, over its accompanying effect in diminishing the rate of conduction of the impulse. These effects are predominantly on the ventricular muscle, and to a less extent on the junctional tissues. Occasionally a more significant effect can be exerted on a vulnerable, diseased His-Purkinje system depressing A–V conduction and precipitating ventricular fibrillation. Schwartz and Jezer [7] produced transient ventricular fibrillation in two patients with A–V dissociation by intravenous quinidine, and Sprague and Davis [8] reported a fatality with ventricular fibrillation and A–V dissociation in the course of quinidine therapy in an individual with an already depressed atrioventricular conduction system caused by previous digitalis

medication. Often following coronary occlusion impaired function of the His-Purkinje system may be latent, or else so slight and transient as to escape detection even by the electrocardiogram. This was probably true in our case since 7 grains of intravenous quinidine would not produce complete A–V dissociation in the absence of previous damage of the conduction system. Thus the patient had a perfect set-up for ventricular fibrillation, i.e., a hyper-irritable ventricular focus plus an impaired A–V conduction system. Quinidine further depressed the conduction mechanism to provoke this fatal rhythm.

Since it is frequently impossible to predetermine the presence of disease of the bundle tissues, the routine prophylactic administration of quinidine following acute coronary artery occlusion will always be a potentially hazardous procedure. There has not been sufficient evidence to substantiate the premise that quinidine may prevent sudden death from ventricular fibrillation following acute myocardial infarction. On the contrary, the drug under these conditions may become a powerful noxious agent and, as in this case, enhance the development of the fatal rhythm it was intended to forestall. Only when the acute myocardial reaction has subsided are we justified in risking quinidine, for then there is not present the marked myocardial irritability of the acutely infarcted area and we can reasonably accept electrocardiographic evidence of absence of conduction defects as indicating a healthy conduction system. In the above case the drug not only incited, but also perpetuated a malignant circus movement in a heart muscle made susceptible by occult involvement of the A–V conduction system.

The immediate terminal mechanism in quinidine intoxication is apparently controversial. Levine [9] showed experimentally in cats that the immediate cause of death from quinidine was a marked central depression of the respiratory mechanism, and that the heart continued to beat for two minutes after complete respiratory failure without evidence of ventricular fibrillation in most of the cases. Smith [10] believes the immediate cause of death to be cardiac standstill due to depression of both S–A and A–V nodes. However, Davis and Sprague in their fatal case observed evidence of circus movements in the ventricle of the nature of fibrillation, accompanied by auricular standstill, and the cardiac action continued for several minutes after signs of life were absent. In our case ventricular fibrillation was the terminal mechanism and persisted for six minutes after all clinical signs of life were absent.

Conclusion

A case of sudden death during the intravenous administration of quinidine sulphate for ventricular tachycardia following acute myocardial infarction is reported. The mechanism of death as recorded electrocardiographically was ventricular fibrillation.

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7. Schwartz, Sidney B., and Jezer, Abraham: The action of quinine and quinidine on patients with transient ventricular fibrillation, Am. Heart Jr., 1934, ix, 792.
8. Davis, David, and Sprague, Howard B.: Ventricular fibrillation—its relation to heart block, report of a case in which syncopal attacks and death occurred in the course of quinidine therapy, Am. Heart Jr., 1929, iv, 559.
9. Gordon, Burgess, Matton, Marcel, and Levine, S. A.: The mechanism of death from quinidine and a method of resuscitation; an experimental study, Jr. Clin. Invest., 1925, i, 497.
10. Smith, H. L., and Boland, E. W.: Treatment of auricular fibrillation with quinidine and strychnine, Jr. Am. Med. Assoc., 1939, cxiii, 1017.

EDITORIAL

THE RELATION OF SPECIFIC IMMUNITY TO RECOVERY FROM PNEUMOCOCCUS PNEUMONIA TREATED WITH THE SULFONAMIDES

THE remarkably successful results obtained clinically in the treatment of pneumococcus pneumonia with the sulfonamide drugs have stimulated interest in the mechanism of their action, and in their influence on the development of immunity to this organism.

Earlier studies by Whitby [1] and others of the effect of sulfapyridine on pneumococci in vitro showed that in concentrations such as can be obtained in the animal body, it exerts a bacteriostatic effect, inhibiting the growth of the organisms without actually destroying them. In higher concentrations an actual bactericidal action may be manifested. This action is not exerted immediately. In a freshly inoculated culture containing the drug in effective concentration, there is active multiplication, which at first is equal to that in the controls. It is only after about six hours that multiplication is inhibited.[2, 3] It is evident, therefore, that the action of the drug is not that of a simple germicide, but that it interferes with growth in some more subtle way. McIntosh and Whitby [2] among others have suggested that it may block the action of some bacterial enzyme. The exact mechanism of its action is not yet settled.

In the animal body the drug behaves in a similar manner.[2] Thus in the peritoneum of a mouse—even if an effective dose of sulfapyridine has been previously administered—pneumococci multiply actively for a few hours and penetrate into and begin to multiply in the blood stream. Then the inhibitory effect of the drug comes into play, and after 24 hours organisms may no longer be demonstrable. In this respect sulfapyridine differs sharply from immune serum in its action, for the latter exerts its effect immediately.

The inhibitory effect of the drug and the arrest of the infectious process is not accompanied by the immediate appearance of phagocytosis, or of other evidences of antibody production. If the drug is stopped prematurely, there may be a flare-up of the infection. If the administration of the drug is continued and the mice survive, after a few days antibodies do appear, and the mice are found to have a substantial active immunity to reinfection. This immunity is specific and limited to the type of pneumococcus with which the mice were originally infected. Whitby found it to be substantially identical in degree with that produced by inoculating mice with a similar quantity of heat-killed pneumococci. The administration of sulfapyridine to

[1] WHITBY, L. E. H.: Chemotherapy of pneumococcal and other infections with 2 (p-amino-benzenesulfonamido) pyridine, Lancet, 1938, i, 1210–1212.

[2] MCINTOSH, J., and WHITBY, L. E.: The mode of action of drugs of the sulfonamide group, Lancet, 1939, i, 431–435.

[3] SPRING, W. C., LOWELL, F. C., and FINLAND, M.: Studies on the action of sulfapyridine on pneumococci, Jr. Clin. Invest., 1940, xix, 163–177.

these vaccinated mice did not affect the speed of development or degree of immunity produced.

It seems probable, therefore, that in the mouse sulfapyridine does not directly kill the organisms, but that it inhibits their growth until the natural defensive forces can come into play. The pneumococci are then eliminated, probably in large measure by phagocytosis.

It has long been recognized that in man specific antibodies appear in the blood in most cases at about the time of spontaneous recovery from pneumonia, on or near the sixth day. It is believed that recovery is brought about by the activity of these substances, particularly by phagocytosis. The aim of treatment by immune serum has been to supply such substances in larger quantity and at an earlier stage of the infection than the patient himself can produce them. There has been doubt, however, as to the part this natural immune mechanism plays in the recovery of patients treated with sulfapyridine.

Patients with lobar pneumonia who are given adequate doses of sulfapyridine early in the disease often show a fall in temperature within 36 hours. At this time, however, there is usually no evidence of antibody formation in the serum. If sulfapyridine is continued, antibodies usually appear a few days later, at about the time their appearance would be expected in patients recovering spontaneously.[4, 5] The sulfapyridine does not demonstrably influence the development of the immune response. The same phenomena have been observed after treatment with sulfathiazole and sulfadiazine.[6]

If administration of sulfapyridine is stopped prematurely in such cases, soon after the temperature has fallen and when no antibodies are demonstrable, there is often a secondary rise in temperature and flare-up of the infection a day or two later, after the drug has been eliminated. In the absence of complications, however, such a relapse rarely occurs if the drug is continued until there has been time for antibodies to develop. This led Wood and Long [4] to suggest that the slow development of antibodies explains these relapses following premature discontinuance of the drug.

If permanent recovery is dependent upon the natural immunity mechanism, it should be possible usually to demonstrate antibodies in the blood. The frequency with which they have been found has varied considerably, depending probably upon the methods used. Thus Kneeland and Mulliken,[7] testing for precipitins, found only four positive out of 19 cases treated with sulfapyridine and 16 positive out of 21 cases treated with sulfathiazole.

[4] Wood, W. B., and Long, P. H.: Observations upon the experimental and clinical use of sulfapyridine. III. The mechanism of recovery from pneumococcal pneumonia in patients treated with sulfapyridine, Ann. Int. Med., 1939, xiii, 612–617.

[5] Finland, M., Spring, W. C., and Lowell, F. C.: Immunological studies on patients with pneumococcic pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 179–198.

[6] Finland, M., et al.: Sulfadiazine: therapeutic evaluation and toxic effects on 446 patients, Jr. Am. Med. Assoc., 1941, cxvi, 2641–2647.

[7] Kneeland, Y., and Mulliken, B.: Antibody formation in cases of lobar pneumonia treated with sulfapyridine, Jr. Clin. Invest., 1940, xix, 307–312.

Other observers,[4, 5] as already noted, have found them more regularly by utilizing other methods, especially agglutination or mouse protection tests. Fox et al.[8] found eventually a strongly positive agglutination test (Sabin method) in 133 out of 144 cases recovering under sulfapyridine treatment. They found Francis' skin test less reliable, as did Haviland [9] in cases receiving sulfapyridine and small doses of serum. Failure to demonstrate antibodies uniformly is not necessarily significant, as this is not always possible in cases recovering spontaneously. This might be owing to lack of sensitiveness of the methods available. Furthermore, the antibodies in the serum represent excess production, and it is quite conceivable that recovery might occur with a production of antibodies so meager as to leave no demonstrable excess in the circulating blood.

The delay in the appearance of antibodies (after apparent recovery) in patients treated with sulfonamide drugs has raised the question as to whether the drugs delay or inhibit the development of active immunity. This is difficult to determine directly in man, but the available evidence tends to show that the drugs neither hinder nor accelerate the process. Recently Curnen and McLeod [10] have tested this point in rabbits. The animals were given a single dose of killed Type 1 vaccine, and half of the group was given sulfapyridine by mouth, during the period of developing immunity. The drug was then stopped and the presence of active immunity was determined by giving at varying intervals intracutaneous inoculations of living culture by Goodner's method. The immunity in the group which had received sulfapyridine was identical with that in the rabbits which had not received it.

If we accept the view that final recovery depends upon the activity of the immune mechanism of the individual and that sulfapyridine merely inhibits multiplication of pneumococci until this can develop, one would expect that the early supplementary administration of immune serum would be beneficial in accelerating recovery and presumably lessening mortality. Some basis for such an assumption may be found in animal experiments. If the dosage of inoculum, drug and immune serum is properly adjusted, mice can be protected by a combination of drug and serum, whereas neither drug nor serum alone would be effective.[9] Probably some summation of their effects might be obtained in man, at least in occasional individual cases. However, this appears to be exceptional, since in the largest and most carefully controlled series of cases, the supplementary administration of serum has not reduced the mortality below that in cases treated only with sulfonamide drugs. Thus Plummer et al.,[11] in a study of 607 cases, reported a mortality of 9.8 per cent

[8] Fox, W. W., Rosi, R., and Winters, W. L.: The Sabin agglutination test and the polysaccharide skin test (Francis) as indices of recovery in pneumonia, Am. Jr. Med. Sci., 1940, cc, 649–655.

[9] Haviland, J. W.: Type 1 pneumococcal pneumonia. Clinico-immunological studies with special reference to the rationale of combined serum and drug therapy, Bull. Johns Hopkins Hosp., 1941, lxviii, 32–50.

[10] Curnen, E. C., and McLeod, C. M.: The effect of sulfapyridine upon the development of immunity to pneumococcus in rabbits, Jr. Exper. Med., 1942, lxxv, 77–92.

[11] Plummer, N., et al.: Chemotherapy versus combined chemotherapy and serum, Jr. Am. Med. Assoc., 1941, cxvi, 2366–2371.

in patients receiving drug and serum; and 9.3 per cent in cases receiving drug alone. (Cases dying in less than 24 hours were excluded from both groups.) Immune serum, if available, should be given to patients who show toxic reactions to sulfonamide drugs or who fail to respond to them in the usual way, since it is known that drug-fast strains exist. However, these observations raise doubt as to the need or advisability of combining serum with sulfonamide drugs as a routine procedure. Further study will be required to determine whether there is any advantage in doing so.

Some attempts have been made to utilize the appearance of antibodies as an indication that treatment with the sulfonamides has been adequate. Francis' skin test, which is quite useful in controlling treatment with immune serum, is said to be unsatisfactory. Fox [8] has recommended the Sabin agglutination test as an indication of effective immunity and believes that a strongly positive reaction warrants discontinuing the drug if the patient has made satisfactory clinical improvement and if complications can be excluded. Other investigators, however, have reported some degree of agglutinating power in the serum of patients who have later died of the disease, and further work will be necessary to determine the dependability of the test.

P. C.

BOOK REVIEWS

Management of the Cardiac Patient. By WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Assistant Professor of Medicine in charge of the Department of Cardiology, Woman's Medical College of Pennsylvania. 705 pages; 23.5 × 16 cm. J. B. Lippincott Co., Philadelphia. 1940. Price, $6.50.

This volume has been written with the practitioner and his problems especially in mind. Although dealing primarily with the treatment of heart disease, it offers briefer discussion of disease entities, methods of diagnosis including electrocardiography and roentgenographic methods, and instructions regarding the performance and interpretation of certain tests, such as the determination of the venous pressure and the measurement of circulation time, etc. The author makes a feature of the presentation of many illustrative cases, with their management and a discussion of what was accomplished. Specific instructions are given in regard to carrying out such procedures as thoracentesis and abdominal paracentesis. One notes the following statement: "Following abdominal paracentesis, it is a good practice to keep the patient in bed until the next day." In heart disease, when abdominal paracentesis is necessary, this seems to be something of an understatement, unless further explanation be given. Some may wonder at the classification of a patient with a blood pressure of 120/90 as hypertensive—no further comment is made on the blood pressure in this patient, and no further recordings are presented.

The most valuable part of this volume is the presentation of the case histories with notes as to the management of the patients concerned, and frank discussion of the results obtained and the diagnostic problems. It should be of considerable help to the busy practitioner who can find similarities between his case problems and those here presented.

W. S. L., JR.

The March of Medicine. Number VI of the New York Academy of Medicine Lectures to the Laity. Introduction by HAVEN EMERSON, M.D. 154 pages; 21 × 14 cm. Columbia University Press, New York. 1941. Price, $2.00.

Like its predecessors in this series, "The March of Medicine," 1941, maintains a high standard of informative material about certain fields of medicine addressed to the laity. The introduction states: "Earlier series have related the systematic progress in conquest of disease, the methods by which physicians become indispensable experts in human salvaging. Here are offered some fruits of contemplation, of reasoned delving into the causes and results of ancient events and almost traditional iconoclasms, and with but one exception all contribute to the pressing preoccupation of the much confused man of today." This series is rather deeper, more philosophical and more difficult to read than the previous series; however, it is also more thought-provoking. To the writer, the most entertaining and interesting lecture is "Paracelsus in the Light of Four Hundred Years" by Henry E. Sigerist. Other distinguished contributors and their lectures are as follows: Alan Gregg, "Humanism and Science"; William Healy, "Psychiatry and the Normal Life"; Irwin Edman, "Philosophy as Therapy"; Oscar Riddle, "The Promise of Endocrinology"; and Francis Carter Wood, "What We Do Know About Cancer."

The New York Academy of Medicine is to be congratulated for continuing these lectures and also for making them available in such an attractive printed form.

J. E. S.

Physical Diagnosis. By WILLIAM NANCE ANDERSON, B.Sc., M.D. 424 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1940. Price, $4.75.

The scope of this book lies midway between the voluminous texts on physical diagnosis and the small handbooks.

The book is divided into three parts. Part I deals with the fundamental principles of physical diagnosis. Proper emphasis is placed upon the importance of a complete history in the systematic study of a case. In this part are discussed the general principles of an examination, inspection, palpation, percussion and auscultation.

Part II deals with the actual method of procedure of a physical examination. Here the proper method for a general complete physical examination is described. Examination of the head, extremities, heart and lungs is stressed. Special systems such as the nervous system are only briefly mentioned.

Part III deals with physical diagnosis in disease. Abnormal physical findings caused by specific cardiac, pulmonary and abdominal diseases are adequately discussed.

The author emphasizes the practical value of mastering the fundamentals of physical diagnosis and points out that the proper interpretation of physical signs and symptoms is the basis for correct diagnosis. He also comments concerning the satisfaction and inspiration derived from the ability to correlate the findings on physical examination with the underlying pathology. The fundamentals of normal and pathological physiology are briefly and clearly discussed with the purpose of explaining the mechanism of production, and interpretation of the various possible findings by physical examination.

Medical students have a tendency to underestimate the need for and importance of performing a careful, thorough physical examination. This attitude has, in a certain measure, been unavoidably aided by the many innovations in all phases of laboratory diagnosis. The author quotes Sir James Mackenzie to illustrate this point: "The seeming exactness of a mechanical device appeals much more strongly to certain minds than a process of reasoning. The sensitive index finger of the experienced doctor can give far more valuable information than all the instrumental methods in the world." Although this statement is not entirely true at the present time, it is still worthy of repetition and should be emphasized in teaching students of medicine.

The fact that there is no bibliography may hamper those readers who wish to refer to the original articles describing various physical findings. A greater number of illustrations would increase the value and understanding of the reading matter. The subject matter is well organized and is simply presented. The style is lucid and promotes easy reading. This book is recommended to the medical student as a brief, practical text on physical diagnosis.

E. T. L.

The A B C of Criminology. By ANITA M. MUHL. 238 pages; 22.5 × 14 cm. Melbourne University Press, Melbourne, Australia. 1941.

This book "is not intended as a text-book of criminology"; the subject matter consists of a series of 13 lectures delivered at the University of Melbourne dealing with practical problems in the field of criminology. The author points out that "crime" and "criminal" are relative terms and feels that it is more correct to use such terms as "offenses against the criminal law" and "offenders against the criminal law." Although the discussion of mental illness is incomplete it should prove of especial interest to persons who have neither time nor inclination to read more extensive texts in psychiatry dealing with the various reaction types.

The problem of stealing by children, adolescents, and adults, as well as the discussion of sex crimes, is interestingly presented through case studies in which many practical therapeutic suggestions are made. With the exception of the chapter on epi-

lepsy, the remainder of the book is more in keeping with the title. There are two interesting chapters dealing with murder, and the author indicates how many murders might have been prevented by the application of present day technics in mental hygiene and psychiatry. Perhaps the most poignant chapter is the one dealing with the reliability of testimony. The final discussion is concerned with a brief review of modern methods of treatment in the field of criminology, and a chapter on the rôle of mental hygiene in dealing with pre-school children and adolescents.

H. W. N.

Cardiac Classics. By FREDERICK A. WILLIUS, M.D., Chief, Section of Cardiology, The Mayo Clinic, and THOMAS E. KEYS, A.B., M.A., Reference Librarian, The Mayo Clinic. 858 pages; 25.5 × 18 cm. C. V. Mosby Co., St. Louis, Missouri. 1941. Price, $10.00.

Dr. Willius and Mr. Keys have presented us with a delightful volume. Starting with Harvey's "Disquisition on the Motion of the Heart and Blood in Animals," written in 1628, the authors present those works of 52 authors that have come to be considered classics among the studies of the heart and circulation. They are largely reproduced in their entirety and a brief biographical sketch of each author is given.

Most physicians give but little time to the study of the development of knowledge in their profession, perhaps because textual matter is not easy to obtain. This volume renders such an excuse untenable for those interested in the heart and circulation. It also provides fascinating reading.

W. S. L., JR.

COLLEGE NEWS NOTES

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. Siegfried Block, Brooklyn, N. Y.
Dr. James D. Bruce, Ann Arbor, Mich.
Dr. Ardrey Whidden Downs, Edmonton, Ala.
Dr. Edward W. Hayes, Monrovia, Calif.
Dr. Frederick E. Hudson, Stamford, Tex.
Dr. H. Leon Jameson, Philadelphia, Pa.
Dr. Henry L. Ulrich, Minneapolis, Minn.

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

John W. P. Love, F.A.C.P., Major (MRC), U. S. Army—"Outline of Laboratory Course" and "Laboratory Manual."

Reprints

Dr. George C. Anglin, F.A.C.P., Toronto, Ont.—4 reprints;
Dr. Irving L. Applebaum (Associate), Newark, N. J.—2 reprints;
Dr. J. Edward Berk (Associate), Philadelphia, Pa.—10 reprints;
Dr. Edward G. Billings, F.A.C.P., Denver, Colo.—1 reprint;
Dr. B. Earl Clarke, F.A.C.P., Providence, R. I.—2 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
John Harper, F.A.C.P., Captain (MC), U. S. Navy—2 reprints;
Dr. Robert F. Ives, F.A.C.P., Brooklyn, N. Y.—1 reprint;
Dr. Enrique Koppisch, F.A.C.P., San Juan, P. R.—1 reprint;
Dr. Perry Scott MacNeal (Associate), Philadelphia, Pa.—1 reprint;
Dr. William E. Ogden, F.A.C.P., Toronto, Ont.—6 reprints;
Dr. Richard Kohn Richards (Associate), North Chicago, Ill.—10 reprints;
Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—3 reprints;
Dr. Sidney Schnur (Associate), Houston, Tex.—12 reprints;
Dr. Leslie McKnight Smith, F.A.C.P., El Paso, Tex.—1 reprint;
Dr. William C. Voorsanger, F.A.C.P., San Francisco, Calif.—1 reprint;
Dr. William A. Winn (Associate), Springville, Calif.—1 reprint;
Dr. Benjamin F. Wolverton, F.A.C.P., Cedar Rapids, Iowa—2 reprints.

Special Gift to the College Library

Dr. H. Sheridan Baketel, F.A.C.P., Jersey City, N. J., has made a gift to the College Library of the following medical books, which are not only of great general interest, but of additional significance because of their age, all of them having been published about a hundred or more years ago:

"The First Lines of the Theory and Practice of Surgery; including The Principal Operations."—Samuel Cooper. Volumes I and II. 4th American Edition, from the 7th London Edition. New York, 1844.

"The Principles and Practice of Surgery, Founded on the Most Extensive Hospital and Private Practice, During a Period of Nearly Fifty Years."—Sir Astley Cooper. Volume I, 1836. Volume II, 1837. Volume III, 1843. London.

"Medical Inquiries and Observations."—Benjamin Rush. Volumes I and III. 3d Edition. Philadelphia, 1809.

"The Study of Medicine."—John Mason Good. Volumes I, II, III and IV. 5th American Edition, from the last London Edition. New York, 1827.

FOURTH ANNUAL ROUND-UP OF EASTERN PENNSYLVANIA MEMBERS OF THE COLLEGE

On February 6, 1942, under the direction of Dr. Edward L. Bortz, College Governor for Eastern Pennsylvania, the Fourth Annual Regional Meeting for this territory was held in Philadelphia with an attendance somewhat in excess of 250. The day's program began with a buffet luncheon at the College Headquarters. The following scientific program was given in the afternoon in the Medical Laboratories of the University of Pennsylvania:

"Recent Studies in Epilepsy."
HAROLD D. PALMER, Professor of Psychiatry, Woman's Medical College of Pennsylvania; Associate in Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pa.

"Contact Infection."
JOHN M. HIGGINS, Associate in Charge of Pediatrics, Robert Packer Hospital, Sayre, Pa.

"Gold Salts and Arthritis."
JOHN LANSBURY, Associate Professor of Medicine, Temple University School of Medicine, Philadelphia, Pa.

"Pneumonia Deaths."
KENNETH E. QUICKEL, Associate Physician on Indoor Medical Staff and Dispensary Physician in Cardiac Clinic, Harrisburg Hospital, Harrisburg, Pa.

"Leukemia."
DANIEL B. PIERSON, JR., Assistant Physician, Lankenau Hospital, Philadelphia, Pa.

"Embolic Occlusion."
DAVID W. KRAMER, Assistant Professor of Medicine, Jefferson Medical College, Philadelphia, Pa.

At the adjournment of the scientific session the group assembled for a social hour, followed by a dinner, at the Union League. Dr. William D. Stroud, Treasurer of the College, was Toastmaster. The dinner meeting was addressed by President Roger I. Lee, Boston; President-Elect, James E. Paullin, Atlanta; Secretary General, George Morris Piersol, Philadelphia; former President, O. H. Perry Pepper, Philadelphia; Captain A. H. Allen of the Philadelphia Navy Yard; and Captain Henry L. Dollard, Commanding Officer of the Philadelphia Naval Hospital. Among special guests were Dr. Roy R. Snowden, College Governor for Western Pennsylvania; Dr. Lewis B. Flinn, College Governor for Delaware; Dr. Louis Krause, College Governor for Maryland; Dr. George H. Lathrope, College Governor for New Jersey; Dr. Wallace M. Yater, College Governor for the District of Columbia; Dr. William Pearson, Dean of Hahnemann Medical College; Dr. William Pepper, Dean of the University of Pennsylvania School of Medicine; Dr. William H. Perkins, Dean of Jefferson Medical College; and Dr. George H. Meeker, Dean Emeritus of the University of Penn-

sylvania Graduate School of Medicine. A quartet from the Philadelphia Orpheus Club provided music and songs, and Mr. Henry W. Doughton provided stories. Many Fellows and Associates of the College were present from New Jersey and Delaware.

These regional meetings are of significant value in that they bring the local members closer together, expand general good Fellowship, and provide an opportunity to keep the members informed of the activities of the College in a more intimate fashion.

Dr. Lea A. Riely, F.A.C.P., Oklahoma City, College Governor for Oklahoma, reports that the Oklahoma City Internists held a Washington's Birthday Clinic at the University Hospitals, Oklahoma City, on February 23, 1942, with the following program, and with 77 physicians registered, 45 of whom were from outside of Oklahoma City. Under similar auspices these clinics have been held in Tulsa, Chickasha and Ada, Oklahoma.

Allergy Clinic
Dr. P. M. McNeill, F.A.C.P., Oklahoma City.
Diabetes Clinic
Dr. Bert F. Keltz, F.A.C.P., Oklahoma City.
Cardiac Clinic
Dr. W. W. Rucks, Jr., F.A.C.P., Oklahoma City.
Clinical Pathological Conference
Dr. Hugh Jeter, F.A.C.P., Oklahoma City.
Luncheon Forum
Conducted by: Dr. A. W. White, F.A.C.P., Dr. L. J. Moorman, F.A.C.P., Dr. George A. LaMotte, Dr. Lea A. Riely, F.A.C.P., all of Oklahoma City.
Chest Clinic
Dr. Floyd Moorman (Associate, A.C.P.).
Clinic on Anemias
Dr. Wann Langston, F.A.C.P., Oklahoma City.
Arthritis Clinic
Dr. William K. Ishmael, Oklahoma City.

Dr. Andrew C. Woofter, F.A.C.P., Parkersburg, W. Va., has been elected President of the Parkersburg Academy of Medicine.

Dr. Harry Mandelbaum, F.A.C.P., Brooklyn, N. Y., has been appointed Attending in Medicine at the Jewish Sanitarium for Chronic Diseases.

Dr. Julius H. Comroe, F.A.C.P., York, Pa., is the internist in the Cardiovascular Division of the Army Medical Examination Center "D," at the Harrisburg, Pa., Military Post. He has been serving also as the internist for the Pennsylvania State Medical Advisory Board No. 4, which comprises nine counties.

Dr. William H. Watters, F.A.C.P., has been appointed to the department of Legal Medicine in Harvard Medical School. Prior to this appointment, he resigned an appointment as one of the Medical Examiners of Suffolk County (Boston) and had previously resigned as Professor of Preventive Medicine in Boston University School of Medicine. The new appointment will consist largely of summer postgraduate activities and will enable him to devote more attention to his winter practice in Miami.

Associated with him in Miami is his son, Dr. Preston H. Watters, F.A.C.P., who during the summer is Instructor in Medicine at the University of Rochester and a Visiting Physician at the Strong Memorial Hospital.

The 38th Annual Congress on Medical Education and Licensure was held in Chicago, Ill., February 16–17, 1942. Among the speakers were:

Dr. Jonathan C. Meakins, F.A.C.P., Montreal, Que.—"The Effect of the War on Medical Education in Canada";

Ross T. McIntire, F.A.C.P., Rear Admiral (MC), U. S. Navy, The Surgeon General—"Medical Education from the Standpoint of the Navy Medical Corps";

George F. Lull, F.A.C.P., Colonel (MC), U. S. Army—"Current Medical Personnel Problems of the Army";

Dr. Thomas Parran, F.A.C.P., The Surgeon General, U. S. Public Health Service—"Needs of the Public Health Service for Medical Personnel in National Defense Activities";

Dr. Walter E. Vest, F.A.C.P., Huntington, W. Va.—"Citizenship as Related to Licensure."

James C. Magee, F.A.C.P., Major General (MC), U. S. Army, The Surgeon General, has ordered the members of the Northwestern University's General Hospital Unit No. 12 to active duty at Camp Custer, Mich. The Northwestern Unit is the first of the three hospital units organized in Chicago to be called to active duty. Among the College members who were called to duty with this unit were:

M. Herbert Barker, F.A.C.P., Lieutenant Colonel (MRC), U. S. Army;
Richard B. Capps (Associate), Major (MRC), U. S. Army;
Eugene L. Walsh (Associate), Major (MRC), U. S. Army;
Richard H. Young, F.A.C.P., Major (MRC), U. S. Army.

The 4th Annual Forum on Allergy was held in Detroit, Mich., January 10–11, 1942. This meeting consisted of a series of study groups, symposia, lectures and educational exhibits. Among the leaders of the study groups were:

Dr. Karl D. Figley, F.A.C.P., Toledo, Ohio—"Perennial Allergic Coryza";
Dr. Herbert J. Rinkel, F.A.C.P., Kansas City, Mo.—"Food Allergy";
Dr. J. Warrick Thomas, F.A.C.P., Cleveland, Ohio—"Ocular Allergy";
Dr. Orval R. Withers (Associate), Kansas City, Mo.—"Gastro-intestinal Allergy, Cyclic Vomiting and Beginning Migraine";
Dr. Frank R. Menagh, F.A.C.P., Detroit, Mich.—"Neurodermatitis in Adults";
Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio—"Physical Stigmata of Allergy";
Dr. Ralph Bowen, F.A.C.P., Houston, Tex.—"Asthma in Children";
Dr. Theodore L. Squier, F.A.C.P., Milwaukee, Wis.—"Food Allergy";
Dr. Homer E. Prince, F.A.C.P., Houston, Tex.—"Mold and Smut Allergy";
Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill.—"Asthma in Adults over 45 Years of Age";
Dr. Leon Unger, F.A.C.P., Chicago, Ill.—"Allergic Conjunctivitis";
Dr. John Sheldon (Associate), Ann Arbor, Mich.—"Allergic Conjunctivitis."

At the Symposium on Food Allergy, Dr. Clark P. Pritchett (Associate), Columbus, Ohio, discussed "The Dietary Management," and at the Symposium on Hay Fever, Dr. McKinley London (Associate), Cleveland, Ohio, discussed "Pollen and Pollen Extract in Oil."

At the Annual Forum Luncheon, January 11, Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio, presented the Forum Gold Medal to Dr. William W. Duke, F.A.C.P., Kansas City, Mo. Later in the afternoon Dr. Duke delivered the Annual Forum Lecture. His subject was "The Beginning of Clinical Allergy in the United States."

Dr. Harry L. Alexander, F.A.C.P., St. Louis, Mo., delivered a special lecture to the Forum entitled "The Broader Aspects of Allergy."

The following Educational Exhibits were presented by members of the College:

"Demonstration of Twenty Roentgenograms of the Chest in Cases First Thought to Be Asthma but Which Proved to Be Something Else"—Dr. George L. Waldbott, F.A.C.P., Detroit, Mich.;

"Insects Which Act as Antigens: Caddis and May Flies"—Dr. Karl D. Figley, F.A.C.P., Toledo, Ohio;

"Insects Which Act as Antigens: Daphnia"—Dr. Karl D. Way (Associate), Akron, Ohio;

"The Story of the Asthmatic Child"—Dr. Ralph Bowen, F.A.C.P., Houston, Tex.;

"The History of Asthma"—Dr. Leon Unger, F.A.C.P., Chicago, Ill.

"Ocular Allergies"—Dr. J. Warrick Thomas, F.A.C.P., Cleveland, Ohio.

On January 9, Pre-Forum Clinics on Allergy were conducted at the University Hospital in Ann Arbor, Mich. Among those who presented clinics were:

Dr. Herman H. Riecker, F.A.C.P., Associate Professor of Internal Medicine—"Bronchiectasis, Allergic Factors";

Dr. Udo J. Wile, F.A.C.P., Professor of Dermatology and Syphilology and Chairman of the Department of Dermatology and Syphilology—"Drug Eruptions";

Dr. Cyrus C. Sturgis, F.A.C.P., Professor of Internal Medicine, Director of Simpson Memorial Institute, and Chairman of Department of Internal Medicine—"Hemorrhagic Diathesis";

Dr. John M. Sheldon (Associate), Assistant Professor of Internal Medicine—"Preparation of Fungus Extracts."

Dr. Hugh J. Morgan, F.A.C.P., Nashville, Tenn., a Colonel in the Medical Reserve Corps of the U. S. Army, has been called to active duty. Dr. Morgan will serve as Head of the Subdivision of Medicine, Professional Services Division, in the office of the Surgeon General, Washington, D. C.

The 57th Annual Session of the Mid-South Post Graduate Medical Assembly was held in Memphis, Tenn., February 10–13, 1942. Among the speakers were:

Dr. Francis M. Rackemann, F.A.C.P., Boston, Mass.—"The Causes of Asthma, Their Diagnosis and Treatment";

Dr. Irvine H. Page (Associate), Indianapolis, Ind.—"The Nature and Treatment of Arterial Hypertension";

Dr. David C. Wilson, F.A.C.P., Charlottesville, Va.—"Practical Methods of Diagnosis in Nervous and Mental Diseases";

Dr. Frank N. Wilson, F.A.C.P., Ann Arbor, Mich.—"Angina Pectoris";

Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y.—"The Chronic Diarrheas";

Dr. Clifford J. Barborka, F.A.C.P., Chicago, Ill.—"Medical Management of Gall-bladder Diseases."

At the recent annual meeting of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., in Washington, D. C., Joseph F. Siler, F.A.C.P., Colonel (MC), U. S. Army, Retired, was elected President, and Merritte W. Ireland, F.A.C.P., Major General (MC), U. S. Army, Retired, was elected Secretary.

Dr. Burrell O. Raulston, F.A.C.P., Los Angeles, spoke on "Newer Sulfonamides," and Dr. Howard F. West, F.A.C.P., Los Angeles, spoke on "Diabetics Today" at a

meeting of the Western section of the American Laryngological, Rhinological and Otological Society at Los Angeles, Calif., February 1, 1942.

Dr. Peter T. Bohan, F.A.C.P., Kansas City, Mo., spoke on "Casual Factors in Angina Pectoris and Coronary Infection" at a recent meeting of the Pratt County (Kan.) Medical Society.

Dr. Felix J. Underwood, F.A.C.P., Jackson, Miss., was one of the speakers at the recent annual meeting of the Louisiana Public Health Association in New Orleans.

Charles F. Craig, F.A.C.P., Colonel (MC), U. S. Army, Retired, has been appointed a member of the Editorial Board of the Journal of the National Malaria Society, which is a new annual periodical.

Dr. William C. Menninger, F.A.C.P., Topeka, spoke on "The Psychiatrist in Relation to the Examining Boards" at a recent meeting of the Missouri-Kansas Neuropsychiatric Association held in Topeka, Kan. Dr. Alexander R. MacLean, F.A.C.P., Rochester, Minn., spoke on "Postural Psychoneuroses" at the banquet of this meeting.

Dr. Frank R. Menne, F.A.C.P., Portland, Ore., was the guest speaker at the recent annual meeting of the Seattle Surgical Society. Dr. Menne spoke on "Lymphosarcoma of Small Intestine with Report of Two Cases Receiving Surgical Intervention."

Dr. Anton J. Carlson, F.A.C.P., Chicago, Ill., delivered the first annual A. C. Helmholz Lecture, January 16, 1942, under the auspices of the University of Wisconsin Medical Society at Madison. The subject of Dr. Carlson's address was "Some Unknown Problems in the Physiological Pathology of Aging."

Dr. Harold M. Coon, F.A.C.P., Madison, has been elected a member of the Board of Directors of the Wisconsin Hospital Association.

Dr. Seale Harris, F.A.C.P., Birmingham, Ala., spoke on "The Food Factor in Winning the War" at a meeting of the Northwestern Division of the Medical Association of the State of Alabama in Florence, January 28, 1942.

Among the guest speakers at the 10th Annual Midwinter Post Graduate Clinics of the Colorado State Medical Society held in Denver, February 19–21, 1942, were:

Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio—"Chemotherapy in Infectious Diseases";

Dr. Benjamin H. Orndoff, F.A.C.P., Chicago, Ill.—"Endometriosis: Its Relation to Sterility and Other Conditions of the Female Pelvis";

Dr. Edward H. Hashinger, F.A.C.P., Kansas City, Mo.—"Hypothyroidism."

Dr. Marine R. Warden, F.A.C.P., Danville, Ill., spoke on "Radiology" at a recent meeting of the Fountain-Warren County (Ind.) Medical Society at Kramer.

Dr. Alexander B. Gutman, F.A.C.P., New York, N. Y., spoke on "Biochemical Aids to Roentgenologic Problems in the Differential Diagnosis of Bone Disease," and

Dr. Cornelius P. Rhoads, F.A.C.P., New York, N. Y., spoke on "Recent Studies in the Production of Cancer by Chemical Compounds" at the Eastern Conference of Radiologists held in New York City, January 23–24, 1942.

In order to acquaint the public with the best methods for the prevention of disease and promotion of health, the Town Club, of Oklahoma City, Okla., with the approval of the Oklahoma County Medical Association, presented a series of free health talks. The program included:

January 7—"Colds, Influenza and Pneumonia," Dr. Floyd Moorman (Associate);
February 4—"Heart Disease: Its Prevention and Care," Dr. Bert E. Mulvey, F.A.C.P.;
March 4—"The Brain in Health and Disease," Dr. C. J. Fishman, F.A.C.P.;
April 1—"Your Weight and How to Control It," Dr. Bert F. Keltz, F.A.C.P.

Dr. Cecil J. Watson, F.A.C.P., Minneapolis, Minn., was one of the guest speakers at a postgraduate course in Therapeutics conducted by the University of Manitoba Faculty of Medicine in Winnipeg, February 11–13, 1942. Dr. Watson spoke on "Some Physiological and Clinical Aspects of Jaundice."

Dr. Joseph H. Barach, F.A.C.P., Pittsburgh, Pa., addressed the Indiana County Medical Society, at Indiana, Pa., on February 12, 1942. His subject was: "The Treatment of the Complications of Diabetes."

The Hermann M. Biggs Memorial Lecture which is held annually in Hosack Hall at The New York Academy of Medicine under the auspices of the Committee on Public Health Relations will be delivered this year on Thursday, April 2nd, at 8:30 p.m., by Dr. James S. McLester, F.A.C.P., Professor of Medicine at the University of Alabama, Chairman of the Council on Foods and Nutrition of the American Medical Association, and Chairman of the Subcommittee on Medical Nutrition of the National Research Council. The subject of the lecture will be "Nutrition and the Nation at War."

Dr. José Bisbé, F.A.C.P., General Secretary of the Medical Federation of Cuba, Havana, reports that that organization has organized a Committee on Medical Preparedness in connection with the war, under the direction of Dr. Pedro Fariñas. This Committee is integrated by delegates from all important medical societies of Cuba and with organizations closely related to the medical profession, such as those representing nurses, pharmacists, women's social clubs, the Reporters Association, etc.

The following sub-committees have been set up to accomplish the objectives of this Committee:

Sub-committee on Foods and Nutrition
Sub-committee on Medical First Aid
Sub-committee on Pharmacy
Sub-committee on Preventive Medicine and Public Health
Sub-committee on Technical Training
Sub-committee on Medical Mobilization

A series of conferences has been initiated, the first one having taken place at the Academy of Sciences on January 23, with a remarkable attendance. Dr. Moises Chediak and Dr. Guillermo García López made the presentations on "National Organization of Blood Transfusion Services" and "Importance of the Official Measures Aiming to Guaranty a Correct Diet for the Population in All Possible Emergencies," respectively.

The Cuban Committee on Medical Preparedness is undertaking a complete reorganization of their records; questionnaires have been sent out to the four thousand physicians belonging to the Federation to have the physicians properly classified, and a study is being made of those measures which will insure an adequate diet and a proper stock of medicines. Courses are being organized for the technical training of young physicians, nurses and women, and special attention is being given to measures for preventive medicine.

Dr. Bisbé, as General Secretary of the Medical Federation of Cuba, expresses the earnest desire and firm determination of the doctors of Cuba to coöperate with the medical profession of the United States in this emergency to the total extent of their ability.

Reduction in Dues to Members on Active Military Service

The American College of Physicians has gone on record, through its Board of Regents, to help and to alleviate the burden of dues of members called to active military service. Regulations have been established whereby the dues of all Associates and Fellows entering upon military service are automatically reduced to $10.00, this amount to entitle the members to fully active and participating membership as before. Furthermore, if the reduced dues should be a burden a member may apply by letter to the Committee on Public Relations of the College, stating the situation, and the Board of Regents may authorize further reduction or the full remission of dues.

The primary necessity at present is the winning of the War. A secondary, but nevertheless important, object should be to preserve our American Institutions. Comparable organizations on the European Continent lie buried with their martyrs. Our American Institutions must have some support to carry on during this War. It is merely asked that those members who can afford to do so shall continue paying some dues. The College, after all, has been doing a great deal for the War effort, and will do more so far as its means provide. For more than a year, the College has foreseen the present needs and was chiefly responsible, financially and by administration, for setting up an office for the classification of 28,000 physicians, including internists, pediatricians, medical Reserve Officers and general practitioners, with respect to their qualifications and availability for military service. This work is still going on, and there are more than 35,000 additional physicians to be evaluated. This work has been carried on in the office of our President-Elect, Dr. James E. Paullin, of Atlanta. One of the objectives of this work has been to see that physicians are used according to their qualifications and experience—to have an internist doing Internal Medicine, not Surgery, and vice versa. The College, during February, organized and presented a series of Postgraduate Lectures for the Medical Officers in a large Naval Hospital, and are expecting to extend this program to other large military hospitals, thus affording an opportunity for the Medical Officers to obtain advance training, which, in War times, is often not available to them otherwise. Still another contribution that was made more than a year ago was an appropriation of $10,000.00 for a rather complicated military research problem in connection with blood plasma, the work being carried out by Professor Cohn, of Harvard. This appropriation was made through the National Research Council, Committee on Medicine, at a time when no funds were being made available by the Federal Government. Although the project itself has been of great value, action by the College in making this appropriation has more significance from the standpoint that it had prime importance in bringing forth adequate appropriations from the Government for such projects in the present and future.

Many members of the College are making real contributions to the War effort by directing numerous and important committees in the National Research Council and other bodies in Washington. The College is justifying itself in civilian practice, in postgraduate education and in many other directions. It fully merits the continued support of all members who can afford to make some contribution in dues. Those in

a more favorable position may feel a patriotic obligation not only toward the College but toward other American Institutions to increase their zeal and their loyalty, and to make their contributions in dues to help make up for those on active military service who must, of necessity, in some instances, be carried free.

Conservation of Scholarly Journals

The American Library Association created this last year the Committee on Aid to Libraries in War Areas, headed by John R. Russell, the Librarian of the University of Rochester. The Committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after the first World War was that of completing foreign institutional sets of American scholarly, scientific, and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the Committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. As far as possible they will be completed from a stock of periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the coöperation of subscribers to this journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project or concerning the value of particular periodicals to the project should be directed to Wayne M. Hartwell, Executive Assistant to the Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.

American Psychiatric Association Opens Contest for Emblem Design

Dr. J. K. Hall, F.A.C.P., Richmond, Va., President of the American Psychiatric Association, has announced a contest for the design of an emblem for that society. The emblem will be used in the centennial celebration in 1944 of the American Psychiatric Association, which is the oldest organization of medical specialists in the country.

Artists, art teachers and students are invited to compete. Prizes amounting to a total of $500 will be awarded. Three prizes of $100 each will be awarded for the three best drawings, selected by a jury which includes an architect, a painter and a sculptor. From these three drawings, the Council of the Association will select the one which they consider most suitable for their purpose. This drawing will receive an additional award of $200 and will become the property of the Association. All remaining drawings will be returned.

The design may be executed in any medium; it should be rectangular and preferably vertical. To facilitate handling, the size of the mat should be 11 by 14 inches. Artists are requested not to place their signatures on the face of the drawing or in a place which is concealed under the mat. The full name and address of the contestant should appear on the reverse side.

Drawings should be sent to the American Psychiatric Association, 9 Rockefeller Plaza, New York City, and should reach that office not later than April 15, 1942.

Inquiries concerning the general ideas of the contest, or details of the history or activities of the American Psychiatric Association, which might be helpful to the artist, are to be addressed to the Chairman of the Committee on History of Psychiatry, Dr. Gregory Zilboorg, 14 East 75th Street, New York City.

The artist is free to use any ideas he deems suitable. However, in order that the design should represent the aims of the American Psychiatric Association, its purpose in the study of mental diseases, and its social and cultural importance, it is suggested that the artist write to Dr. Zilboorg for the explanatory folder containing this information.

Errata

On page 182 of the January, 1942, issue of this journal appeared a report on the Regional Meeting of the Illinois members of this College at Chicago on December 6, 1941. Dr. Fred Drennan took the place of Dr. Ralph C. Brown as one of the clinicians in the Clinico-pathologic Conference.

Postgraduate Course No. 9, Gastro-Intestinal Diseases, Withdrawn

It was with regret and disappointment on the part of the Director and of the College that Postgraduate Course No. 9, Gastro-intestinal Diseases, at the University of Chicago, April 6–18, 1942, under Dr. Walter L. Palmer, had to be withdrawn on March 10. The war situation with greater pressure than usual at the institution, with a greater undergraduate teaching load, coupled with the fact that the registration for this course was comparatively small, is responsible for the action taken. Dr. Palmer expresses the hope that when the war emergency has passed, he and his associates will again have the opportunity to coöperate with the College in its postgraduate program.

OBITUARIES

DR. SAMUEL WALDRON LAMBERT, SR.

Dr. Samuel Waldron Lambert, Sr., was born in New York City, June 18, 1859, and died at his home, 101 East 72 Street, New York City, on Monday, February 9, 1942, at the age of eighty-two years. He was the son of Dr. Edward W. Lambert and the former Martha Waldron. His father was a prominent New York physician and his brothers, the late Dr. Alexander Lambert, personal physician and intimate friend of President Theodore Roosevelt, and Dr. Adrian V. S. Lambert, surgeon of New York City.

Dr. Lambert was a Trustee and former President of the New York Academy of Medicine. He received his A.B. degree from Yale University in 1880 and Ph.B. from Yale University in 1882; M.D. from the College of Physicians and Surgeons in 1885. After the completion of his Internship at Bellevue Hospital, he attended clinics in Berlin, Munich, and Vienna for two years. On his return to New York in 1889, Dr. Lambert began the practice of medicine and obstetrics and in the next year he introduced bedside teaching of medical students at the Midwifery Dispensary founded by himself and Dr. James Markoe. His influence in the organization of hospital services and particularly their integration with the teaching activities of the medical schools in this City grew progressively. In its first year the

newly formed Dispensary trained more than two hundred students and in 1892, because of its success, it was amalgamated with the Society of the Lying-in Hospital.

Dr. Lambert served as Attending Physician to Nursery and Childs Hospital, 1890–1898; Midwifery Dispensary, 1890–1893; New York Lying-in Hospital, 1892–1903; New York Hospital, 1896–1909; and St. Luke's Hospital, 1906–1929. He was Professor of Applied Therapeutics, 1903–1919, Columbia University College of Physicians and Surgeons; Professor of Clinical Medicine, 1904–1929, Columbia University College of Physicians and Surgeons, and Dean of Columbia University College of Physicians and Surgeons from 1904–1919.

Dr. Lambert was Consulting Physician to the Ruptured and Crippled Hospital, French Hospital, Bronx Hospital, St. Luke's Hospital, Fifth Avenue Hospital, New York Orthopedic Hospital, Presbyterian Hospital, Reconstruction Hospital, Neurological Institute, St. Vincent's Hospital, Home for Incurables, Colored Orphan Asylum, White Plains Hospital, Southside Hospital, Laurence Hospital, St. John's Riverside Hospital and Tarrytown Hospital. He was also a Trustee of the Roosevelt Hospital from 1904–1919.

Years ago Dr. Lambert proposed the creation of a medical center in this City, a proposal which was enthusiastically received. He prepared a program for the establishment of such a center in 1915 and saw its realization thirteen years later in the building of the Medical Center. He was also a leader in the fight for city cleanliness and the long struggle against the Volstead Act's limitations on the prescription of liquor for medicinal purposes. Dr. Lambert, at the time he was President of the New York Academy of Medicine, was leader in the formation of the Committee of Twenty on Street and Outdoor Cleanliness, and was a supporter of moderate drinking as an aid to good health, a subject on which he gave many dissertations; he was a vigorous opponent of prohibition and particularly fought the Congressional limitation on physician's rights to prescribe liquor to patients. Under the Volstead Act physicians could not prescribe more than one pint of liquor to a patient every ten days, which Dr. Lambert called "a legislative lie." He fought this law from 1922 until the Celler-Copeland bill ended it in March 1933. He brought a test case against it which went to the Supreme Court, where he lost the fight by a five to four decision but he continued to urge a national organization of physicians to fight the Eighteenth Amendment and the Volstead Act. In carrying the test case through the courts, he acted as President of the Association for the Preservation of Constitutional Rights.

As Dean of Columbia University College of Physicians and Surgeons, during the World War, Dr. Lambert devoted his efforts and those of the Medical College to turning out the greatest possible number of physicians for service with the American Forces. At the suggestion of and in coöperation with the Government, the College graduated the class of 1919 two years ahead of time, giving the Government the services of more than one hundred additional physicians.

Dr. Lambert engaged in non-medical, as well as medical writings, was a book collector and developed a large library, a considerable portion of which was devoted to angling literature, especially Waltoniana and Cottoniana. His writings included a volume written with Dr. George M. Goodwin entitled "Medical Leaders," a criticism of Dickens, "When Mr. Pickwick went Fishing," and many shorter articles published in the Bulletin of the New York Academy of Medicine and in various issues of "The Proceedings of the Charaka Club." He also contributed twenty-seven medical papers.

Dr. Lambert received an honorary M.A. from Yale University in 1905 besides one from Columbia University. He was a member of the following medical societies: the Charaka Club, the Clinical Society of New York, Practitioners Society of New York, Alumni of Bellevue Hospital Society, Medical and Surgical Society of New York, Association of American Physicians and the American Gastro-Enterological Society. He was an original member of the Interurban Clinical Club, founded by Sir William Osler in 1905, which was devoted to advances in medical teaching and research. He was also a member of the Association of American Medical Editors and Authors, the New York Academy of Medicine, New York County Medical Society, New York State Medical Society, Fellow of the American Medical Association, and Fellow of the American College of Physicians since 1931.

Among his clubs were the Century Association, Grolier Club, Union Club, Racquet and Tennis Club, University, Yale, Graduates Club of New Haven, South Side Sportman's, Oquossoc Angling Association of Maine, Megantic Fish and Game Corporation and Psi Upsilon, Nu Sigma Nu, and Alpha Omega Alpha fraternities.

Dr. Lambert married Elizabeth Willets on October 21, 1893, who survives him. Also surviving, besides his brother, Dr. Adrian V. S. Lambert, are a son, Dr. Samuel W. Lambert, Jr., two daughters, Mrs. Gillet Lefferts and Mrs. J. Ogden Bulkley.

CHARLES F. TENNEY, M.D., F.A.C.P.
Governor for Eastern New York.

DR. GEORGE WASHINGTON HALL

On October 25, 1941, medicine lost a grand gentleman and a great physician in the person of George Washington Hall. Dr. Hall was born in Crawfordsville, Indiana, in 1869, graduated from Wabash College in 1890, and from Rush Medical College in 1893. He received both his B.A. and M.A. degrees while at Wabash. At the age of 24 he was on his way to various European clinics to increase his knowledge.

After graduation in medicine, Dr. Hall became an associate of Dr. Daniel Brower who was, at that time, Professor of Materia Medica at Rush. In the same office with Dr. Brower was Dr. E. Fletcher Ingals, Professor of Diseases of the Chest and of the Nose and Throat. It was, therefore, quite natural for Dr. Hall to become primarily an internist.

In 1902, he was an instructor in the Department of Medicine and in 1907 assistant professor.

Dr. Brower gradually turned his attention to the field of neuropsychiatry in which he became eminent. Dr. Hall followed this change and from 1911 advanced step by step until he became professor of nervous and mental diseases at Rush.

He was attending neurologist on the staff of Cook County Hospital from 1907 until 1918, later transferring to the Psychiatric service. In 1916, he was appointed senior neurologist at St. Luke's hospital which position he continued to hold until his death. In 1932 he was president of the medical staff of St. Luke's Hospital.

During his sojourn in Europe, he studied at the National Hospital, Queens Square in London and attended clinics in Berlin, Vienna and Munich. He was a member of the American Neurological Association, the Neurological Society of Chicago, past president of the Central Neuro-Psychiatric Association, and member of the Board of Governors of the Institute of Medicine of Chicago. He had been a Fellow of the American College of Physicians since 1930.

During later years, his life was interrupted by repeated attacks of coronary occlusion. In spite of the advice of his family, friends, physicians and others, he continued in the active pursuit of a busy practice and literally died with his boots on while attending a meeting of the Central Neuro-Psychiatric Association.

Dr. Hall was primarily a physician who had become an excellent neurologist and neuro-psychiatrist. His early training made him very appreciative of the close relationship of general disease to nervous and mental change. His students, interns, residents and associates recognized in him a fine doctor whose knowledge was beyond the strict limitations of his own field. He was wont to check the patient's general condition, his blood pressure, pick up an auricular fibrillation as a basis for a cerebral attack, call the turn on a questionable syphilitic, recognize the association of the less obvious blood dyscrasias, lung abscess or general infection to the nervous and mental changes which might be at the moment outstanding.

He made much of his hunches. His uncanny arrival at a correct diagnosis on clinical grounds at times belied the value of numerous laboratory procedures. He was pushed by competition with excellent men both within his own hospital group and without. He was at all times respected and admired by these men.

Dr. Hall was an inspiration to many a young man. A pat on the back, an invitation to golf, to bridge, to poker carried with it the unspoken suggestion—"it is my duty and my pleasure to help him along a bit."

He enjoyed life to the fullest, had a host of friends, young and old, enjoyed their companionship, was respected and admired by them and will be remembered with the affection that comes from recognition and admiration of an understanding that was more human than usually touches those who reach high peaks.

Dr. Hall was a grand sportsman. He was not only an ardent golfer but a good one and in his heyday could putt like a wizzard, drive straight but not long, approach close to the pin and make tough going for even the best. He received much pleasure from his golf and the associates of his golfing days. As he facetiously remarked more than once, he was known as a golfer among the neurologists and as a neurologist among the golfers.

He played a fine hand at bridge or poker and after the tournaments sought out a corner and turned in a pretty demonstration of his "extramural" activities.

There was always a good story on tap for his rounds at St. Luke's, at the tournaments in the evening, at the medical societies, at banquets, at his various clubs or within the privacy of his own home.

There is nothing unkind that one can say of George Hall. His death will be a real loss to Chicago medicine and to medicine in general. Others will come but not excel this fine gentleman of good humor;—kindly, thoughtful, gentle, honest and stimulating. He has gone to his rest covered with happy remembrances of his urge to help others and the satisfaction that comes from a duty well performed.

His burial service was so simple, so honest and so personal that it would have made George Hall very happy. From his throne above, he surely can look down and say, "It was a grand old earth, I was always happy and they liked me."

GEORGE H. COLEMAN, M.D., F.A.C.P.

DR. CHARLES HATCH STODDARD

Dr. Charles Hatch Stoddard, F.A.C.P., was born in East Troy, Wisconsin, 1869. Following premedical work for three years at the University of Wisconsin he was graduated from the University of Illinois College of Medicine in 1892. During the next two years he was occupied with postgraduate study in Vienna and Strassburg. Participation in medical responsibilities in his community included the following: He was the first Medical Director and Superintendent of the Bluemound Sanatorium in 1907; a member of the first Wisconsin Committee of the International Congress on Tuberculosis, 1908; for many years he was a member of the staff at such hospitals as Columbia, Mount Sinai, St. Mary's, Milwaukee County and the Milwaukee Hospital. He served the Wisconsin Anti-Tuberculosis Association as a member of the Board of Directors, later as Vice-president for nineteen years, and as President in 1931 and 1932, following which he was Recording Secretary from 1933 to his death. Twice he was Vice-president of the Milwaukee Academy of Medicine; he was President in 1927 of the Milwaukee County Medical Society. In 1916 he was a member of the House of Delegates of the American Medical Association. He was made a Fellow of the American College of Physicians in 1926. During the first World War he served as a Major in the Medical Corps in the Wisconsin National Guard. Death came December 17, 1941, of chronic nephritis.

Those whose acquaintance with Dr. Stoddard dates back many years recall the geniality of his early days in the profession. He established himself in Milwaukee in the early nineties. Several decades before this, his father, also a physician, erroneously concluding that the trend of commercial life led to the interior of the State, settled in practice in a small community, then finally established himself in LaCrosse, where his son spent his earliest years. It was perhaps natural for him to remain in the State of his birth and to cast his lot in its metropolis—now far outgrown his pioneer father's anticipation.

Although in the early years of his professional life Dr. Stoddard's health was undermined and necessitated a break in practice, he was able to resume work, and continued unremittingly up to a year or two before his death. With the knowledge that he had an illness that spelled his doom, no word of complaint was uttered; his stoicism was uncanny and almost unreal to those associated with him; his family was not to know the agony that was his.

Dr. Stoddard's fine, upright character, his broad educational background, his inherent refinement of manner and action all served to single him out as one endowed by nature with the qualities that must make and adorn the successful physician. He instilled confidence; his integrity won the attachment of friend and patient; he was dignified but not unbending; his unassuming attitude toward his confreres won their respect.

No one can gain a respected position in a community without having earned this regard. And surely it may be said of Dr. Stoddard that the many who treasure his memory do so from a sense of honest appreciation of the man's genuine worth.

ARTHUR J. PATEK, M.D., F.A.C.P.

DR. CHARLES CLAGETT MARBURY

Dr. Charles C. Marbury, F.A.C.P., Washington, D. C., died December 10, 1941, of coronary thrombosis, aged 71.

Dr. Marbury was born at Upper Marlboro, Maryland, July 11, 1870. He attended the Charlotte Hall Academy, received his B.A. degree from Saint John's College, Annapolis, in 1890, and graduated in medicine from Georgetown University School of Medicine in 1893. From 1903 to 1925 he was Professor of Clinical Medicine at his Alma Mater, and from 1925 to the time of his death, Professor of Clinical Medicine Emeritus. He was a veteran of the Spanish-American and World wars; since 1928, member of the Consulting Staff of the Central Dispensary and Emergency Hospital; member of the Board of Visitors and Governors of Saint John's College, 1924 to 1938; former President of the Clinical Society of the District of Columbia and of the Clinico-Pathological Society; member of the Medical Society of the District of Columbia; Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1928.

Dr. Marbury was a quiet man, of pleasing personality and was well liked.

MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

DECEMBER 14, 1941

The regular autumn meeting of the Board of Regents was held at the College Headquarters, December 14, 1941, starting at 10:15 a.m. President Roger I. Lee presided, and the following were in attendance:

Roger I. Lee.....*President*
James E. Paullin.....*President-Elect*
D. Sclater Lewis.....*First Vice-President*
Samuel E. Munson.....*Third Vice-President*
William D. Stroud.....*Treasurer*
George Morris Piersol.....*Secretary-General*
Francis C. Blake
Reginald Fitz
Charles T. Stone
J. Morrison Hutcheson
Walter W. Palmer
O. H. Perry Pepper
James D. Bruce
T. Homer Coffen
Ernest E. Irons
Jonathan C. Meakins
Hugh J. Morgan
Maurice C. Pincoffs
Charles H. Cocke
John A. Lepak.....*General Chairman, Twenty-sixth Annual Session*
Warren Thompson.....*Member, Committee on Nominations*
Edward L. Bortz.....*Chairman, Advisory Committee on Postgraduate Courses*

Mr. E. R. Loveland, Executive Secretary, acted as Secretary.

The Secretary, Mr. Loveland, read abstracted Minutes of the meetings of the Board held at Boston during April, 1941. These were approved with a correction by Dr. Paullin of "financial support of the National Research Council."

The Secretary read communications of regret from Drs. William J. Kerr, Egerton L. Crispin, Gerald B. Webb, David P. Barr and Thomas T. Holt, members who were unable to be in attendance.

Other communications included:

(1) Report that President Lee had appointed Dr. Wallace M. Yater, Governor for the District of Columbia, as official College representative at the installation of the new President of the American University, October 19, 1941;
(2) A letter from Dr. Hugh S. Cumming, President of the Gorgas Memorial Institute, notifying the College that the By-Laws of the Institute provided "that the President of the American College of Physicians shall be a member ex officio of that Institute";

(President Lee had been unable to attend the meeting in November, due to the notice not reaching him in time.)

(3) A report that Dr. Francis G. Blake had been appointed by President Lee, October 25, 1941, to succeed Dr. James H. Means, resigned, as one of the College representatives on the Advisory Council on Medical Education;

(4) A digest of letters received from Dr. Cecil M. Jack, Governor for Southern Illinois, F. G. Norbury, of Jacksonville, and Third Vice President Samuel E. Munson, of Springfield, concerning division of the Governors' territories in Illinois.

(No action was taken because Dr. LeRoy H. Sloan, Governor for Northern Illinois, had not yet filed his report, map and suggestions. Therefore, this item shall be placed on the agenda for the next Regents' meeting.)

Dr. George Morris Piersol, as Secretary-General, reported as follows:

(1) The deaths of 32 Fellows and 3 Associates since last meeting of this Board:

Fellows:

Albee, George M.	Worcester, Mass.	August 10, 1941
Alvarez, John Arthur	Houston, Tex.	October 19, 1941
Baird, Raleigh William	Dallas, Tex.	July 13, 1941
Bishop, Louis Faugeres, Sr.	New York, N. Y.	October 6, 1941
Burns, Gerald Ross	Halifax, N. S., Can.	November 16, 1941
Campbell, Edward Everett	Columbus, Ohio	July 4, 1941
Cheney, William Fitch	San Francisco, Calif.	April 10, 1941
Compton, Marion Lee	Augusta, Ga.	March 27, 1941
Dailey, Michael A.	M.C., U. S. Army	October 27, 1941
Darling, Ira A.	Torrance, Pa.	October 10, 1941
Fairbanks, Warren Horace	Freehold, N. J.	August 5, 1941
Fordham, George	Powellton, W. Va.	October 4, 1941
Friedenwald, Julius	Baltimore, Md.	June 8, 1941
Hall, George Washington	Chicago, Ill.	October 25, 1941
Joachim, Henry	Brooklyn, N. Y.	August 18, 1941
Jones, Austin Byron	Kansas City, Mo.	September 3, 1941
Jones, Clement Levi	Springfield, Ohio	August 2, 1941
Kaufman, Isadore	Philadelphia, Pa.	August 11, 1941
Kinlaw, W. Bernard	Rocky Mount, N. C.	July 24, 1941
Krauss, Allen K.	Providence, R. I.	May 12, 1941
Lord, Frederick Taylor	Boston, Mass.	November 4, 1941
Mohler, Henry K.	Philadelphia, Pa.	May 16, 1941
Moor, F. Clifton	Tallahassee, Fla.	February 18, 1941
Olmsted, George Kingsley	Denver, Colo.	June 25, 1941
Paige, Wendell Heath	Brownwood, Tex.	February 14, 1941
Riley, William Henry	Battle Creek, Mich.	August 24, 1941
Stem, Leon Thayer	Sarasota, Fla.	May 15, 1941
Strietmann, Wm. Hurley	Oakland, Calif.	July 14, 1941
Syman, Louis Lawrence	Springfield, Ohio	July 16, 1941
Talley, James E.	Lima, Pa.	July 3, 1941
Wiener, Joseph	Asbury Park, N. J.	September 8, 1941
Wilson, W. Henry	Joliet, Ill.	May 16, 1941

Associates:

Kieser, Henry Samuel	Reading, Pa.	July 11, 1941
Morgan, Mark Tad	M.C., U. S. Army	October 8, 1941
Stephens, Doran J.	Rochester, N. Y.	March 19, 1941

(2) Additional Life Members since the last meeting of this Board (4, making a grand total of 171, of whom 16 are deceased, leaving a balance of 155):

Beaumont S. Cornell	Fort Wayne, Ind.
Walter J. Wilson, Sr.	Detroit, Mich.
Lillian Lydia Nye	St. Paul, Minn.
Ira Dixson	Stockbridge, Mass.

Dr. Piersol proceeded to report as Chairman of the Committee on Credentials. He reviewed the work of the Committee and the candidates for membership. On motion by Dr. Piersol, seconded by Dr. Fitz, and regularly carried, it was

RESOLVED, that the following group of 132 candidates shall be and are herewith elected to Fellowship (those marked with an asterisk—13—being direct elections; all others being advancements—119—to Fellowship).

Likewise, on motion by Dr. Piersol, seconded by Dr. Fitz, it was

RESOLVED, that the following list of five candidates shall be and are herewith advanced to Fellowship "as of April 19, 1942":

The Committee recommended that 5 of the candidates for Fellowship be first elected to Associateship, and their names were presented in connection with elections to Associateship, which follow.

On motion by Dr. Piersol, seconded by Dr. Fitz, it was

RESOLVED, that the following 100 candidates shall be and are herewith elected to Associateship in the College.

A summary of the recommendations of the Committee was presented as follows by Chairman Piersol:

A. Candidates for FELLOWSHIP:

Recommended for Advancement to Fellowship, 12-14-41	119	
Recommended for Direct Election to Fellowship, 12-14-41	13	
Recommended for Advancement to Fellowship "As of April 19, 1942"	5	137
Recommended for Election first to Associateship		6
Deferred for Further Investigation or Material		32
Rejected		6
		181

B. Candidates for ASSOCIATESHIP:

Recommended for Election	94
Fellowship Candidates Recommended for Election first to Associateship	6
Deferred for Further Investigation or Other Credentials	29
Rejected	26
	155

On motion by Dr. Piersol, on behalf of the Committee on Credentials, seconded and regularly carried, a resolution was adopted dropping from the Roster of the College, in accordance with provisions of the By-Laws, the names of 11 Associates who had failed to present the necessary credentials for advancement to Fellowship within the maximum five-year period.

The following is an analysis on the candidates elected to Associateship on December 13, 1936, this meeting marking the expiration of the maximum five-year term:

Advanced to Fellowship	135
Credentials not presented or inadequate	12
Resigned	5
Deceased	5
	157

Dr. Piersol then presented and discussed the following communications, which had been reviewed by the Credentials Committee:

(1) Dr. E. V. Allen—re South American members.

"It was the feeling of the Credentials Committee that at this particular time it is inopportune to do anything looking toward the extension of College membership in South America, and after deliberation, the Committee moved that because of the present great international emergency nothing be done, but the question be laid on the table to be reopened if and when more favorable and peaceful conditions in the various hemispheres exist."

(2) Dr. LeRoy H. Sloan, Governor for Northern Illinois—no action required.

(3), (4) and (5)—Letters from Drs. Sarah I. Morris, Harold E. B. Pardee and Francis M. Rackemann (Fellows) regarding the revision of inquiry cards distributed about candidates.

"The Committee, after reviewing these communications, was of the opinion that it would be a good plan to modify and revise these cards and add to the card a definite request for specific information. The Credentials Committee suggests that the card contain the following questions: 'Is the candidate personally known to you. If the answer is 'Yes,' please reply to the following questions: Is this applicant's personal qualification satisfactory? Are his personal ethics satisfactory? Are his professional attainments satisfactory? Do you favor his election?'"

"On the inquiry card concerning Associates, the following question would be added: 'Do you believe the candidate will qualify for Fellowship within the five-year period?' The Committee suggests that it confer with the Executive Secretary and adopt a new form."

The report of the Committee on Credentials was accepted as a whole, after President Lee had expressed the appreciation of the Board of Regents to the Committee for its long, hard time-consuming efforts.

The Executive Secretary, Mr. Loveland, reported:

(1) As directed by the Board of Regents during the past year, 1500 copies of the College History had been reprinted and made available for future needs;

(2) A completely revised College Directory had been published and distributed to all members. The Directory contains the names of:

4	Masters
3,465	Fellows
1,202	Associates
4,671	Total

(3) Due to deaths since publication of the Directory, the total membership at the current date, exclusive of new elections, is:

4	Masters
3,452	Fellows
1,201	Associates
4,657	Total

Dr. James E. Paullin, Chairman of the Committee on Public Relations, presented the following report:

"This Committee met on December 13, 1941, at 2:00 p.m., at the College Headquarters, with Dr. Roger I. Lee and Dr. James E. Paullin, Chairman, present. The Committee recommends that the following resignations be accepted:

Dr. James A. Butin (Associate), Chanute, Kan.
Dr. Frank Bryant Cutts (Associate), Providence, R. I.
Dr. Morris A. Hankin (Associate), New Haven, Conn.
Dr. Edward C. Humphrey (Associate), Harrodsburg, Ky.

On recommendation of the Committee and by regularly adopted resolution, specific cases were disposed of concerned with the dropping from the Roster of 2 Fellows for delinquency in dues of two or more years' standing, the deferment of action on 1 resignation and the waiver of dues for 4 members who are ill and out of practice. Another resolution was adopted providing for disciplinary action in connection with charges of unethical conduct and violation of the ethics of the American College of Physicians preferred against a member.

"*Communications:*

"The Committee recommends:

"The communication of Dr. Rudolf Schindler in regard to organization of Gastroscopy be filed as information;

"That the communication of Dr. N. W. Faxon of the American Hospital Association and the National League of Nursing Education be filed as information.

"There being no further business, the Committee adjourned.

Respectfully submitted,

JAMES E. PAULLIN, *Chairman*
Committee on Public Relations"

On motion by Dr. Paullin, regularly seconded and unanimously carried, individual resolutions were adopted approving of each recommendation of the Committee on Public Relations and of the report as a whole.

President Lee proceeded with the agenda of the Board of Regents and called for the report of the Committee on Preparedness. Dr. James E. Paullin, Chairman, presented the following report:

"The Committee on Preparedness of the American College of Physicians met at the College Headquarters on December 13, 1941. Those present were Dr. Ernest E. Irons, Dr. Roger I. Lee, Dr. Edward L. Bortz and Dr. James E. Paullin, Chairman.

"On December 15, 1940, the Board of Regents of the American College of Physicians appropriated $2,500.00 to be used by the Medical Committee of the National Research Council in evaluating physicians who had filled out the questionnaire of the American Medical Association stating their qualifications either as internists, pediatricians or general practitioners of medicine. The National Research Council thought that this work could be done under the supervision of the College better than directly through the Research Council.

"We have received from the A.M.A. the names of 74,096 physicians to be evaluated. Of this number we have evaluated 27,950, divided as follows:

"We have completely evaluated 11,383 internists,
5,100 pediatricians,
1,750 Medical Reserve Officers,
9,717 General Practitioners.

"The large group which we are just now beginning to evaluate consists of 46,092 general practitioners. These men, generally speaking, are located in the small towns

and small cities of most of the States, and it is very difficult for our consultants to obtain accurate information concerning them. However, up to the present time, we have information concerning 9,717 of this number. In other words, we have approximately 36,000 of these left to be evaluated.

"In order to accomplish this work, it was necessary to purchase the following equipment:

1 steel filing cabinet for A. C. P. card file and correspondence	$ 42.00	
1 typewriter desk	55.00	
2 chairs (1 typist's chair and 1 side chair)	25.94	
1 Royal typewriter (with extra long carriage)	117.05	
2 steel files, 8-drawers each for cards	118.80	$ 358.79

"We have also had to purchase the following supplies:

Office supplies (carbon paper, second sheets, typewriter ribbons, etc.)	$ 63.55	
Postage and Express	73.97	
Stationery and Printing	168.10	305.62

"To carry on the work, it has been necessary to engage the services of one secretary since the 19th of December, 1940, and one typist for a period of seven months, at a total expenditure of salaries to date of:

Jewel Lancaster, December 19, 1940, through Nov. 19, 1941	$1,119.38	
Ruth Hatcher, February 4, 1941, through September 19, 1941	627.50	1,746.88
TOTAL EXPENSES		$2,411.29
Bank Balance, 12–10–41		88.71
		$2,500.00

"The Medical Building Company has donated to us the use of the necessary space in its building and has furnished us heat, light, water, without any charge.

"It is the opinion of your Committee that this work which the College has undertaken at this particular moment will be of the greatest value to the Board of Procurement and Assignment Service under the Federal Security Administration. We feel confident that the foresight of the College in making this evaluation possible has prevented a delay of at least six or eight months in our Medical Preparedness Program. From past experience, it seems to me that it probably will take another three or four months to complete our files, and it is recommended that the minimum figure of $500.00 be appropriated to complete this job.

"As you undoubtedly know, all of the reports which have been made to me have been in confidence. Certain code numbers have been utilized in keeping the identity of the Consultants unknown to anyone except me. This information appears on each individual's card in code. Since all of this information is confidential, it is necessary that the cards be considered in the same manner. In view of this fact, it is recommended by the Committee on Preparedness that the cards, including the filing cabinets that contain them, be turned over to the Regional Office of the Procurement and Assignment Committee, which will be located in Chicago, for use by this Committee in obtaining physicians for Military and Civilian duty.

"The Committee on Preparedness wishes to take this opportunity of thanking the Governors of the College, the members of the College, and all of the Consultants who helped so unselfishly in making this part of the program possible. We would also like to thank the American Medical Association for their hearty coöperation in this endeavor.

Respectfully submitted,

JAMES E. PAULLIN, *Chairman*
Committee on Preparedness"

STATISTICAL ANALYSIS OF EVALUATIONS

States	Internists	Pediatricians		General Practitioners		Med. Res. Evaluated
		Evaluated	Data Insuff. for Eval.	Evaluated	To be Evaluated	
Alabama	101	59		839		133
Arizona	44	19		210		
Arkansas	78	32			611	
California	853	312			3,750	
Colorado	124	52			589	
Connecticut	215	111			787	7
Delaware	15	9		128		2
Florida	156	54			819	176
Georgia	196	105			944	215
Idaho	10	4		180		
Illinois	738	340			3,425	
Indiana	221	105			1,936	
Iowa	169	60		1,294		
Kansas	114	41			716	
Kentucky	135	73		1,044		
Louisiana	167	67		647		208
Maine	37	14		333		5
Maryland	275	122		1,065		16
Massachusetts	529	223			1,577	60
Michigan	396	176			1,771	
Minnesota	310	94			1,278	
Mississippi	73	35			585	93
Missouri	387	127			1,837	
Montana	29	9		191		
Nebraska	110	36			712	
Nevada	6	2			35	
New Hampshire	22	15			270	1
New Jersey	309	209			1,766	25
New Mexico	12	8		166		
New York	2,102	1,019			8,227	150
N. Carolina	166	77			750	159
N. Dakota	32	8		228		
Ohio	664	276			3,072	
Oklahoma	123	58		700		
Oregon	81	27		547		
Pennsylvania	873	457			4,091	57
Rhode Island	69	37			290	6
S. Carolina	76	45		519		108
S. Dakota	20	7			216	
Tennessee	173	82			923	286
Texas	372	190			2,108	
Utah	22	19		196		
Vermont	29		12	236		1
Virginia	187	95			997	24
Washington	91		42		821	
West Virginia	98	40			659	
Wisconsin	187	83		1,194		
Wyoming	4	4			117	
D. C.	183	63			414	18
Totals	11,383	5,100	54	9,717	46,092	1,750

Internists evaluated to date, 12–10–41	11,383
Pediatricians evaluated to date, 12–10–41	5,100
Med. Res. Officers evaluated 12–10–41	1,750
General Practitioners evaluated 12–10–41	9,717
Total number of physicians evaluated	27,950

We were asked to evaluate	74,096
We have evaluated	27,950
To be evaluated	46,146

(Of this last number approximately 8,000 have been evaluated but the states in which they are listed have not been completely evaluated as yet.)

DR. PAULLIN: "The Board of Procurement and Assignment Service operates under the Federal Security Administration. This Board was appointed by a resolution signed by the President of the United States. We operate under the OPM and the Committee on Health and Medical Care, which is headed by Dr. Irvin Abell, and which is now the policy determining committee under the OPM; ours is the Committee that does the work. The Board of Procurement and Assignment has about ten or fifteen subcommittees which work in conjunction with the Board. This Board is the logical one to receive our reports and the benefits of our work. It is the agency that can use this information with effect. Previously, the Surgeon General of the Army was restricted to a considerable extent because no man could get into the Army if he was thirty-five years or over, except under undue circumstances. We hope to help this Committee in determining the military needs of the Government by establishing a pool of one thousand Reserve Officers. If the Surgeon General sends in a request to the Army for twenty internists, we will send him a list of forty, and from that he can choose men who have said they will volunteer; if he wants two hundred men, we will send him a list of four hundred who are capable of being war surgeons. When he takes them out of that pool, it is our business to keep the pool full all the time, so his needs will be supplied.

"Along with that, there is an effort to protect the civilian population, to see that moderate medical care is given to those people with a moderate amount of curtailment of some of their activities.

"Thirdly, we are attempting through the Medical Education Committee to determine the hospital and teaching needs of all medical schools and all hospitals, and they are asked to coöperate by cutting their supply of medical officers as low as possible. Since practically all teaching institutions have frozen units, or hospital units which have been frozen up until last Monday, those units are released because war has been declared, and all teaching institutions now have been advised that they must revise their list of teaching personnel, eliminate those units that were frozen. Hospital units are now liable to be called to active duty.

"There are a lot of other problems up for consideration. This is a vital question with us, particularly with the College. If you will look very carefully each week in the Journal of the American Medical Association, you will find the details printed of all of this. Every week the deliberations of the Procurement and Assignment Board will be published. The Procurement and Assignment Board will meet next Thursday with the Medical Preparedness Committee of the American Medical Association in Chicago, and after that whatever announcement comes will be available in the next issue of the Journal, and we hope at that time to get the machinery in operation for the utilization of this information which the College has already accumulated to speed our national medical defense more rapidly than it has ever been done before, and to put the right peg in the right hole."

PRESIDENT LEE: "The College has received a great deal of credit through this work by Dr. Paullin. It has been a one-man job. He has devoted a tremendous amount of time and energy to it, and as a reward of his services, he is now going to receive a greater burden of responsibility. The College is proud to be represented by Dr. Paullin on this national committee. It must be a great satisfaction to the Regents and every Fellow of the College that this College got started long before the

Government upon this difficult program, and now we are going to see the fruition of that work. Dr. Paullin now has left out of the original appropriation of $2,500.00 by the College a small sum of about $89.00. He spent much more than that out of his private purse, to say nothing of his time. He has a job to finish up, and if it is agreeable to Dr. Paullin, I should hope that someone of the Regents would be willing to move that a further appropriation of up to $1,000.00 be given for the continuation of his work."

Dr. Pepper reported that the Finance Committee would have a recommendation to cover this item.

On motion by Dr. O. H. Perry Pepper, seconded by Dr. Charles H. Cocke, and regularly carried, it was

RESOLVED, that the location of the cards and files, when the work is completed, be turned over to the Regional Office of the Procurement and Assignment Committee, which will be located in Chicago, for use by this Committee in obtaining physicians for military and civilian duty; also that when Dr. Paullin's evaluation office is closed, other fixtures may be disposed of and the money realized thereon returned to the College; also that the Board of Regents conveys its heartiest thanks to Dr. Paullin.

PRESIDENT LEE: "At this time, it would seem appropriate to have a report from Dr. O. H. Perry Pepper on the activities of the Committee on Medicine of the National Research Council. Sometimes when that Committee meets, I am not sure whether it is a meeting of the Regents of the College or of the Committee on Medicine, because of the large number of representatives from our College."

DR. PEPPER: "Mr. President. I have nothing to report that is not already familiar to the Regents. Our first activities were directly advisory to the Surgeons General in a variety of different fields. We prepared manuals and we wrote the standards of physical examination. The Committee on Medicine has eight or nine subcommittees and the American College of Physicians is widely represented on them. More recently the project that the College started, namely, the giving of money for research service desired by the armed forces, has been taken over by the Government through the establishment of the Office of Scientific Research and Development, with the appropriation of considerable millions of money. The activities of these committees of late have been largely devoted to the evaluation of the many hundreds of research projects that have come in, evaluations of them then to be forwarded to the National Research Council, Committee on Medical Research, under the Chairmanship of Dr. Alfred Newton Richards, where the final decision as to whether funds requested from the Office of Scientific Research and Development for the carrying out of these researches is made. A million or more dollars has already been allocated, and several more millions are available. A constant flow of these research projects is still coming in. Some are initiated by individuals, some by committees that have been cognizant of a need; others have been requested directly by one or another of the armed forces, or some division of the Surgeons General's offices. For example, there was a surprising need of information on various aspects of malarial control, malarial treatment and malarial knowledge, and some hundred thousand dollars have been allocated for that. I am not familiar, because of the secrecy that surrounds aviation, tank and chemical warfare fields, with the exact details of their projects, but I do know that considerable sums of money have been allocated there, so that the activities of your Board of Regents on these committees have shifted to this new type of work. No doubt there will be additional fields opening up.

"A new committee on which there are several members of your Regents has just been formed to develop certain new anti-infection agents, study of the problem, and they are being properly tried out.

"This College allocated $10,000.00 to be used within one year upon recommendation from the National Research Council Committees and approval of the Ex-

ecutive Committee of this Board. $5,000.00 was allocated to Dr. Cohn's work on purified albumin, blood albumin as a blood substitute in transfusions. That money was made available and has proved very useful and has brought the College much credit. The other $5,000.00 has not been allocated, and it is now my recommendation that that offer now be considered expired."

President Lee then called for the report of the Advisory Committee on Postgraduate Courses, Dr. Edward L. Bortz, Chairman.

DR. BORTZ: "Mr. President and members of the Board of Regents—soon after your President appointed this Committee, a meeting was called and a skeletal outline of the courses was drawn up, and this outline sent to the Executive Committee of the College and to the Committee on Educational Policy of the Board of Regents, with the request that they make suggestions for alterations, additions or deletions. Upon receipt of the answers, the Committee wrote to the directors that had been selected, and these men returned promptly their acceptances to act as organizers for these courses and made very enthusiastic statements in support of this activity by this College. The work of the Committee got away to a good start. The men promptly got into action and prepared preliminary statements concerning the content of the courses, following which the 'General Bulletin,' or preliminary announcement of these courses, was published. The members of the Advisory Committee have all been very active and have received much help from Dr. Hugh J. Morgan and members of the Committee on Educational Policy, and from the College Officers available in Philadelphia. During the last two months, details have been increasing in number to the point where your Chairman practically had to be in daily contact with the Executive Secretary. Many conferences have been held. The General Bulletin was distributed to all members of the College, and within a very short time registrations began coming in. Already at this time, Course No. 1 in Allergy under Dr. Robert A. Cooke is filled to capacity, as is also Course No. 10, Internal Medicine, under Dr. Cecil J. Watson at the University of Minnesota. Registration in other courses is developing satisfactorily (Dr. Bortz then read the number registered for each course).

"Acting on a resourceful suggestion by Dr. Francis G. Blake and approved by the Board of Regents, the Executive Secretary is engaged in obtaining advance copies of suggested reading and informal reading lists from each director for publication in an early issue of the 'Annals of Internal Medicine,' in order that all members of the College may be given the benefit of knowing what constitutes the most important and pertinent literature available bearing on these subjects.

"There have been many interesting and flattering comments and letters received by the Executive Office on the work of the College in the field of postgraduate education. Throughout the South, members have decried the fact that there are no courses available during the summer months. This is something for the Regents to study in the future. Just how much influence the present national situation will have on the courses we cannot say, but it is the opinion of your Committee that everything possible will be done to see that these courses are carried through to a successful conclusion.

"Certain thoughts come to mind regarding the possibility of offering opportunities for men in the service, physicians who are not necessarily members of the College, to participate in courses where there is not yet a completed enrollment. We have contacted all the College Governors, asking them to stimulate their local clienteles and membership to enroll."

Dr. Pepper inquired how the College fares financially on these courses, whether the College contributes or gains.

SECRETARY LOVELAND: "Ordinarily the College expends $500.00 or more beyond the income for these courses. The entire registration fee collected from each member is turned over in full to the director of the course. The College finances the organization of the courses, publication of the bulletins and registration expenses. Last

year one of the Directors, Dr. E. V. Allen, refused to accept the honorarium but the College paid all the local expenses, including guest instructors. However, there was a credit balance created and unused."

PRESIDENT LEE: "These courses have been in general very extraordinary, and Dr. Bortz and his Committee have been very adroit in organizing the different types of courses. As their experience increases, they are finding out what our Fellows really want, and I think eventually they will have some very valuable data. We are very grateful to Dr. Bortz for the amount of labor he has put into this. The College is a perfectly relentless boss. It works its people and says occasionally 'Thank You,' but nothing more than that. This is the third Committee that has done a tremendous amount of work—the Committee on Credentials, the Committee on Preparedness and the Committee on Postgraduate Courses. We shall now have the report of the Committee on Educational Policy, Dr. Hugh J. Morgan, Chairman."

DR. MORGAN: "Mr. Chairman, the Committee on Educational Policy has taken pride in what has been done by Dr. Bortz and his Committee, and I would like to point out to the Regents that here in the middle of December there are 145 registrants for these courses. That is something new, something that always has been hoped for—that these courses would be organized and gotten underway before the December meeting of the Board of Regents. Whether or not the war is going to make it difficult for the consummation of the plan is beside the point at the moment. Certainly this Committee has done a splendid job.

"The only other matter that the Committee on Educational Policy would like to bring before the Regents has to do with the efforts that we have made in the past year and a half to make some contribution in the work of continuing education for men in the service. You will recall that at the last meeting the matter of organizing programs to be taken into areas was discussed. Apparently the plan did not meet with wholly favorable acceptance and was abandoned. We are trying to continue operating on that objective. It occurred to us that possibly something could be done about the library facilities of military hospitals where reference books could be made available. In the last war, it was impossible to get any of that sort of thing and no information was available, except by word of mouth from one of the seniors in the service. It was almost impossible to get information at all. Your Committee has been in communication with the Surgeon General's Office, through Captain Davis and Colonel Hillman, and we are informed that there is a basic allowance for the provision of medical journals for hospitals of five hundred beds or larger, service hospitals, and we have been supplied with the list of journals, twenty in number. We immediately discovered that the list did not contain our own 'Annals of Internal Medicine.' Also, there is a list of some sixty or seventy textbooks which constitute the 'basic allowance for books of hospital libraries of hospitals of five hundred beds or more.' The actual type of text and the name of the author are not given in any of these lists, which leads us to feel that some thought directly related to the quantity and quality of the material available would be an important contribution. To that end, your Committee yesterday passed the resolution that 'the Board of Regents authorize the Committee on Educational Policy to communicate with the proper authorities concerning the improvement of medical library service for hospitals of five hundred beds or more.' I would ask the Board of Regents, and I herewith move the adoption of that resolution."

The motion was seconded by Dr. Charles H. Cocke.

DR. PEPPER: "Would it not be a good idea to channel that through the Committee on Medicine. It would then carry the weight of a body that is definitely and officially advisory to the Surgeon General's Office. I think the same information would apply to the larger battleships and units of the Navy."

DR. MORGAN: "I certainly agree, and I will channel it that way."

PRESIDENT LEE: "The resolution confines itself to hospitals of five hundred beds or over, and one wonders if it might be possible to have circulating books and circulating periodicals among smaller hospitals. A great many of these five hundred bed institutions are pretty well provided for, and they can do a good deal about looking after themselves, but some of the smaller ones might need a limited amount of help."

DR. MORGAN: "I will drop 'the five hundred bed designation' and merely say 'service hospitals.'"

Dr. Pepper brought up for discussion the question of whether the College might make a contribution of sending perhaps one hundred copies of the "Annals" to a hundred places to be designated by the Surgeon General. Dr. Morgan and Editor Pincoffs both felt this an expense of some little consequence, and it would be more appropriate to urge the Surgeons General to add the "Annals" to the list of approved journals for service hospitals.

Dr. Paullin suggested that the request should be routed through the Procurement and Assignment Division, Committee on Medical Education and Hospitals, with a recommendation of the Committee on Hospitals going directly to the Surgeon General's Office in the War Department.

In this opinion Dr. Pepper and Dr. Morgan concurred, but pointed out that no change in the resolution would be required, because it reads "to the proper authorities."

The motion was put to a vote and unanimously carried in the following form:

RESOLVED, that the Board of Regents of the American College of Physicians authorizes the Committee on Educational Policy to communicate with the proper authorities concerning the improvement of medical library service in service hospitals.

Dr. Hugh J. Morgan, one of the College representatives on the Conference Committee on Graduate Training in Medicine, reported upon the meeting of that Committee in Chicago during May, 1941. About ten out of a long list of hospitals that applied for evaluation and approval as proper places for resident training were approved and subsequently the Committee's report was accepted by the Council on Medical Education and Hospitals of the American Medical Association. Dr. Morgan said in part, "In my judgment the Conference Committee constitutes a satisfactory medium for the College to express its interest in and to exert its influence in the matter of evaluation of opportunities for resident training. The Conference Committee is comprised of representatives of the Council on Medical Education and Hospitals, the American Board of Internal Medicine and the American College of Physicians. This arrangement is proving to be a satisfactory one from the point of view of all three groups."

A question was asked concerning the work of the Advisory Council on Medical Education.

DR. MORGAN: "This Advisory Council has representatives of the American Hospital Association, the Catholic Hospital Association, the State Boards of Medical Examiners, the American College of Surgeons and the American College of Physicians. I cannot say that the Council has yet accomplished very much, but I have the feeling that it has ambitions and I think it would be to the advantage of this College to remain a member, or to retain membership in this Council, until it is observed what the Council is going to do."

DR. IRONS: "I quite agree with Dr. Morgan. There is a process of evaluation going on in that Council, and we may need quite a little help. It is the kind of help we are going to need which would be the kind furnished by the College representation."

President Lee called for the report of the Committee on Fellowships and Awards, Dr. Francis G. Blake, Chairman.

DR. BLAKE: "I shall report, first, briefly on the Research Fellows who have completed their work since the last meeting of the Board of Regents. Dr. William

Woods Beckman, Dr. Lewis Dexter and Dr. Morris Tager have completed their fellowships. Dr. Beckman, who worked under Dr. van Slyke at the Hospital of the Rockefeller Institute on the chemistry of sterols, has not yet submitted a final report. Dr. Dexter, who worked under Dr. Houssay at Buenos Aires on various aspects of experimental hypertension, has submitted a final report, expressing his gratitude for the fellowship and the value of the experience in Dr. Houssay's laboratory, where all the facilities of the laboratory were made available for his work. Two papers embodying the results of his work have been written and will be submitted to the 'Annals of Internal Medicine.' Dr. Dexter is now at the Peter Bent Brigham Hospital in Boston. Dr. Tager, who worked under Dr. George H. Smith at Yale on staphylococcus infection, has made a final report, accompanied by a reprint covering studies on staphylolysin, carried out under tenure of his fellowship. Dr. Tager is now Instructor in Immunology at Yale. Dr. Homer Swanson, whose resignation on March 1, 1941, has already been reported, has submitted a report that reprints of papers resulting from his studies on Vitamin E deficiency and on fat embolism, under tenure of the fellowship, will be sent as soon as available. Dr. Swanson now holds a resident appointment at the New York Neurological Institute.

"The three fellows appointed at the meeting of the Board, December, 1940, are now at work as follows:

Dr. William Arrowsmith, since July 1, 1941, under Dr. Carl V. Moore, Washington University, St. Louis, on iron metabolism;

Dr. Allan D. Bass, since September, 1941, under Dr. William T. Salter at Yale on hormone factors in neoplastic disease;

Dr. Rulon W. Rawson, since September 1, 1941, under Dr. James H. Means at the Massachusetts General Hospital on thyroid physiology.

"The Committee on Fellowships and Awards has this year received eleven applications for fellowships for the coming year from men who are graduates of a considerable number of universities—the University of California, Stanford, Wisconsin, Harvard, Columbia, Southern California and the University of Vienna. After careful consideration of these applicants, the Committee has selected two whom it considers the two most outstanding of the group:

Dr. James Hopper—Graduate of the University of California Medical School, 1939; internship and residency with Dr. William J. Kerr at the University of California. Dr. Hopper has this year been working on a Cox fellowship at Yale, in the Department of Internal Medicine. He is highly recommended by Dr. Kerr and also by Dr. Mettier of the University of California as one of the outstanding young men of their group that they have had in recent years. He has been in New Haven just a short time, and we feel, as far as we can judge at present, that the recommendations of Drs. Kerr and Mettier are quite just ones. Dr. Hopper makes application for his fellowship to engage in studies of blood volume, particularly a comparison of the carbon monoxide and dye methods of various states, to work in the Department of Medicine at Yale under Dr. Peters.

"The second man that we considered outstanding is:

Dr. Joseph L. Lilienthal, Jr.—Graduate of Johns Hopkins, 1937; internship under Dr. Walter W. Palmer at Presbyterian Hospital, New York City; six months residency at National Hospital, Queens Square, London, and now on the resident staff at Johns Hopkins. He is particularly interested in neurological problems, and he desires to go to Vanderbilt University to work under Dr. Harvey, who is one of our former fellows of some years ago, who worked in England. The particular problems which he wishes to study are those re-

lated to neuromuscular physiology and myasthenia. He is strongly supported by Dr. Philip Bard, Dr. Walter W. Palmer, Dr. W. T. Longcope and several others.

"The Committee on Fellowships and Awards unanimously recommends that Research Fellowships, in the amount of $1,800.00 each, beginning September 1, 1942, be awarded to these two selectees."

On motion by Dr. Blake, seconded by Dr. Irons, and unanimously carried, it was

RESOLVED, that Research Fellowships in the amount of $1,800.00 each shall be awarded, beginning September 1, 1942, to Dr. James Hopper, Jr., whose home is in San Francisco, Calif., for work concerned with a comparison of the carbon monoxide and dye methods of blood volume determination under Dr. John P. Peters of Yale University School of Medicine; and to Dr. Joseph L. Lilienthal, Jr., Baltimore, Md., for work concerned with observations on myasthenia gravis and related problems in neuromuscular transmission in man under Dr. A. M. Harvey in the Department of Medicine at Vanderbilt University School of Medicine, Nashville, Tenn.

DR. BLAKE: "The Committee on Fellowships and Awards held long discussions and experienced considerable difficulty in picking the above two men over two others in the group of eleven, who, perhaps, are almost equally good in accomplishment and promise, and so, after discussion, the Committee wishes to recommend, if it is agreeable to the Regents and the Finance Committee, that a third fellowship be awarded to Dr. Charles P. Emerson, Jr., Graduate of Harvard Medical School, 1937. His hospital training was at Boston City Hospital and at the Thorndike Laboratory. He is highly recommended by every one who has written about him—Keefer, Finland, Castle and others. He wishes to continue and carry along further investigations, and is now concerned with the physical and chemical studies of red blood cells, particularly in relation to problems of hemolytic anemia under Dr. William B. Castle at the Thorndike Memorial Laboratory, Boston.

"Again the Committee unanimously recommends the granting of this fellowship."

On motion by Dr. Blake, seconded and regularly carried, it was

RESOLVED, that a Research Fellowship, in the amount of $1,800.00, beginning September 1, 1942, be awarded to Dr. Charles P. Emerson, Jr., for work concerned with the study of various factors which act in vitro as hemolyzing agents and in animals and man to cause hemolytic anemia under Dr. William B. Castle, Dr. George R. Minot and Dr. T. H. Ham at the Thorndike Memorial Laboratory, Boston City Hospital.

(Secretary's Note: Dr. Emerson was unable to accept this fellowship due to summons to active military duty with the Harvard Base Hospital, but provision was made that he may file application to resume the fellowship following his discharge from service, and that such application will receive special consideration.)

DR. BLAKE: "The Committee on Fellowships and Awards, recognizing that in all probability there may be withdrawals of fellows appointed prior to assuming of fellowships because of call to service with the armed forces, discussed the question of recommending the appointment of a fourth very good man as an alternate, in awarding to him a fellowship to take effect should one of the appointed fellows withdraw prior to the assumption of the fellowship. This fourth man is:

Dr. Carl G. Heller—Graduate of the University of Wisconsin, M.D. and Ph.D., 1940. His hospital training was received at the Wisconsin General, Madison. He is now in Detroit at Wayne University with Dr. Gordon B. Myers. All during his period of study at Wisconsin, both for his Ph.D. and M.D. degrees, he was actively engaged in research largely with Dr. Sevringhaus

and has to his credit a number of publications with Dr. Sevringhaus and later two or three of his own dealing with hormone problems along general lines of work in which Dr. Sevringhaus has been interested. He is highly recommended by Dr. Sevringhaus, Dr. Henry R. Carstens, Dr. Gordon B. Myers and Dr. Walter J. Meek. He seems to be a man of industry and lots of drive, described as a very competent individual. He desires a fellowship to work on the physiological problems of hypo- and hypergonadism in relation to hypo- and hyperpituitarism in human males and females under Dr. Myers at Wayne University.

"The Committee again unanimously recommends the award of this fellowship to Dr. Heller as an alternate."

On motion by Dr. Blake, seconded by Dr. Pincoffs and regularly carried, it was

RESOLVED, that a Research Fellowship of the American College of Physicians, in the amount of $1,800.00, beginning July 1, 1942, be awarded to Dr. Carl G. Heller as an alternate, should there be withdrawals of other appointed fellows, this fellowship to be made for work concerned with the physiological problems of hypo- and hypergonadism in relation to hypo- and hyperpituitarism in human males and females under Dr. Gordon B. Myers at Wayne University, Detroit.

On motion by Dr. Blake, seconded by Dr. Cocke, and regularly carried, it was

RESOLVED, that if during the tenure of his Research Fellowship a fellow resigns because of entrance into service in the armed forces, when such service is completed an application for resumption of his fellowship shall receive special consideration.

DR. BLAKE: "With respect to the Phillips Memorial Award, letters were sent out about the first of November to all Regents and Governors, and to a selected list, as has been done in the past, asking for suggestions and nominations of at least three individuals, arranged in the order of choice, for the Phillips Memorial Award. From this canvass, the Committee received fifty-three nominees over which considerable time has been spent, combing out those who obviously were not very satisfactory nominees and reducing the list down to about fifteen for further consideration. After reviewing the accomplishments and the pertinence of the work of these individuals, taking into consideration the fact that the Award is for work in Canada or in the United States, relatively recent work, either in the field of Internal Medicine or the basic sciences, having relation to Internal Medicine, the Committee on Fellowships and Awards unanimously recommends to the Board of Regents that the John Phillips Memorial Medal for 1942 be awarded jointly to Dr. John Rodman Paul, Professor of Preventive Medicine, Yale University School of Medicine, and Dr. James Dowling Trask, Associate Professor of Pediatrics, Yale University School of Medicine, for their studies on the clinical epidemiology of poliomyelitis, and more particularly for their recent demonstration of the prevalence of the virus of poliomyelitis in feces and its detection in sewage and in flies.

"Dr. Paul was born in Philadelphia, Pa., on April 18, 1893. He received the degree of Bachelor of Arts at Princeton University in 1915 and the degree of Doctor of Medicine at Johns Hopkins University in 1919. He was Assistant in Pathology at Johns Hopkins during 1919–20 and interne at the Pennsylvania Hospital, Philadelphia, from 1920 to 1922. He was Director of the Ayer Clinical Laboratory, Robert Robinson Porter Research Fellow in Medicine and Associate in Surgical Pathology at the University of Pennsylvania from 1922 to 1928. Since 1928 he has been a member of the faculty of Yale University School of Medicine as Assistant Professor of Medicine from 1928 to 1934, Associate Professor of Medicine from 1934 to 1940, and Professor of Preventive Medicine since 1940.

"Dr. Trask was born in Astoria, Long Island, N. Y., on August 21, 1890. He received the degree of Bachelor of Philosophy at Yale University in 1913 and the

degree of Doctor of Medicine from Cornell University in 1917. He was an interne at the Bellevue Hospital, New York, from June, 1917, to May, 1918, and served in the U. S. Army during the World War I, from May, 1918, to December, 1919. He was Assistant Resident Physician at the Hospital of the Rockefeller Institute for Medical Research in New York from 1919 to 1921, Instructor in Medicine at Yale University School of Medicine from 1921 to 1925, Assistant Professor of Medicine from 1925 to 1927, and since 1927 has been Associate Professor of Pediatrics.

"Begun a decade ago at a time when research on poliomyelitis had for many years been more concerned with the experimental disease in monkeys than the natural disease in man, Paul and Trask's earlier work was concerned with studies on the epidemiological, clinical and immunological aspects of abortive poliomyelitis. As a result of these investigations they emphasized the much greater prevalence of the minor or Wickman type of abortive poliomyelitis than had previously been suspected and the probable significance of this generally unrecognized prevalence of minor infections in the spread of the disease. In subsequent work they established the importance of employing recently isolated strains of virus in studying the immunology and pathogenesis of poliomyelitis. Their more recent investigations have been particularly concerned with the method of transmission of the disease. In the course of this work they have shown that monkeys may be successfully infected subcutaneously, intraperitoneally and by way of the gastro-intestinal tract much more readily than had been supposed; that the virus is more easily and frequently recoverable from the stools than from the nasopharynx in both paralytic and abortive cases; and that it is present in the feces not only during the acute stage of the disease but also for weeks after recovery from the acute phase. They have, furthermore, shown that the virus may be isolated from sewage during the course of epidemics, and quite recently have detected its presence in flies collected in the field during epidemics of the disease.

"Undertaken at a time when poliomyelitis was generally if not universally believed to be a contact infection transmitted by way of the upper respiratory tract, Dr. Paul and Dr. Trask's studies of the disease have not only served to reopen the whole question of the epidemiology of poliomyelitis but have also marshalled an impressive body of evidence which would appear to support the idea that poliomyelitis may after all be an 'intestinal disease.'"

On motion by Dr. Morgan, seconded by Dr. Pincoffs and regularly carried, it was

RESOLVED, that the recommendations of the Committee on Fellowships and Awards be approved and that the John Phillips Memorial Medal be awarded for 1942 jointly to Dr. John R. Paul and Dr. James D. Trask, medals to be awarded to each, the names of both recipients appearing on each medal.

Dr. Morgan suggested that the College obtain photographs of all Phillips Medalists for record in the College Archives. Secretary Loveland replied that photographs have been obtained of all previous recipients.

President Lee called for the report of the American Board of Internal Medicine, Dr. Ernest E. Irons, Chairman.

Dr. Irons said he had no formal report to offer, but that the work of the Board is proceeding satisfactorily.

DR. PEPPER: "How have the specialized examinations worked out?"

DR. IRONS: "In general, one could say that the system has been satisfactorily established. The tendency will be, I think, for a very much smaller number of holders of the certificates of the Board to want also some sub-specialty designation. I do not have the figures exactly in mind, but perhaps of all those who are in Cardiology—we circularized at the request of that group—not over ten per cent of them wanted to have another additional ticket on the bottom of their certificates. I think as time goes on it will appear that this rousing demand for sub-specialization will subside. Of course, those who are especially interested in one of these sub-specialties will not be

particularly enthused over this tendency. The Board has made no effort to influence the matter one way or another. Four sub-specialties are now being covered by the Board. We are also going to have a number of requests for recognition of further sub-specialties. The feeling of the Board is that those requests will have to be scrutinized very carefully, and I suspect the Board will move very slowly in the immediate future in these directions.

President Lee called for the report of the Committee on Annals of Internal Medicine, Dr. Walter W. Palmer, Chairman.

DR. PALMER: "As may be seen from the financial statement, the ANNALS is more than self-sustaining. For Volume XIV the surplus was nearly $7,000.00 ($6,947.86). The character of the articles has improved steadily. Your Committee believes the publication of the ANNALS is one of the important functions of the College.

"With the increase in costs of publication the need for reducing the number of pages printed may occur. For the present, your Committee recommends no change be made in the size of the journal.

"The Editor reports a request from a journal called *Medicas,* published in Spanish in New York and distributed to South American countries, to republish entire articles appearing in the ANNALS. It has been the policy of the ANNALS not to permit the publication of entire articles. Most requests for this privilege come from commercial journals. Some consideration to the request on the part of *Medicas* seemed desirable, in view of the good neighbor policy. However, for the present, it would appear wise not to recommend any exception to the general policy until the publication, *Medicas,* has been thoroughly investigated."

President Lee then asked for a report from the Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs.

DR. PINCOFFS: "Mr. President, I have very little to report. In accordance with the decision of the Committee on the ANNALS at its last meeting, the journal is now appearing in two volumes a year, each with its own index. The first of these half year volumes will come out at the end of December. I might say a word in amplification of the question of economy in the ANNALS during the war period. It is quite well realized, with a possible falling off of subscriptions and a probable rise in cost of publication, that the time will come when the size of the ANNALS will have to be reduced, in order to keep from having a deficit. It is, however, so strongly on the credit side at the present time, that it is felt that it will not be necessary to inaugurate a policy of economy in advance of possible handicaps later on. Upon the authority of the Executive Committee of the College, such a reduction or change in policy could be made in the midyear, or at any other time that would be advisable, if that condition should arise."

Secretary Loveland reported that no immediate problems could be foreseen. The present publishing contract extends through June, 1942, and there have already been purchased adequate paper stock and envelopes for the period ending June, 1942.

DR. PEPPER: "I can think of nothing more useful for this College to do than to go into the 'red,' if necessary, in maintaining the present standard of the ANNALS. It would be a mistake to let the decision on the ANNALS be determined by the mere bookkeeping item. We have had a surplus every year for some time. There is no reason to think that we are not going to go on having it, and I would think that the present situation is one where we ought to move forward rather than backward, even if we used some considerable parts of our surplus. With this thought in mind, I recently wrote to Editor Pincoffs and urged him to introduce colored illustrations, which will come into medical publishing as they become better and cheaper, and my thoughts run along that line rather than that of retrenchment."

The meeting at this point recessed at 12:55 p.m. for luncheon.

At the resumption of the meeting, President Lee called for the report of the Committee on Survey and Future Policy, Dr. James E. Paullin, Chairman.

"The Committe on Survey and Future Policy of the American College of Physicians met at the College Headquarters on December 13, 1941, with the following in attendance: Dr. Charles H. Cocke, Dr. Jonathan C. Meakins, Dr. James Alex. Miller, Dr. Hugh J. Morgan, Dr. George Morris Piersol, Dr. Maurice C. Pincoffs and Dr. James E. Paullin, Chairman.

"Your Committee on Survey and Future Policy wishes to submit this report to the Board of Regents:

"A communication from the National Committee to Signalize Benjamin Franklin's Continuing Contribution to American Civilization is read with a great deal of interest. It is recommended that the American College of Physicians coöperate with this Committee and express our willingness to land whatever documents, historical papers and the like which may come into our possession for the furtherance of the purpose of the Committee;

"A communication from Dr. Maurice A. Schnitker, of Toledo, Ohio, President of the American Federation for Clinical Research, requesting that there be a combined or joint meeting of his Society with the American College of Physicians, has been received. It is recommended that we welcome the American Federation for Clinical Research and extend to them an invitation to attend the Morning Lectures and General Sessions of the meeting of the College in St. Paul, April 20–24, 1942. We further suggest that the meetings of the American Federation for Clinical Research, which are contemplated to be held in Minneapolis, take place before the meeting of the College in St. Paul. We feel that the establishment of a friendly relationship with this organization to be beneficial, both to the College and to the organization.

"At a meeting of the Board of Regents on April 22, 1941, a resolution was adopted as follows:

"RESOLVED, that the recommendation of the Committee on Survey and Future Policy, concerning the waiver of dues of members called to active military service, be referred back to said Committee for study and report at the December, 1941, meeting of the Board of Regents.

"In view of the fact that the emergency has passed and that War is now declared, it is recommended to the Board of Regents that all members of the American College of Physicians who are on full-time duty with the armed forces, or who are assigned to other full-time duties concerned with national defense, have their dues reduced to correspond with those which are now effective for those members who are now officers of the Army and Navy, namely, $10.00 per annum.

"It is also recommended that the Board of Regents address a communication to the Procurement and Assignment Board of the Federal Security Administration, attention of the Sub-committee on Medical Education, stating the gratification which comes to the Board of Regents of the American College of Physicians for the proposed program outlined by the Sub-committee for the continuance of medical education of medical officers now in the armed forces as outlined and operative at the present time. The American College of Physicians wishes to offer its full coöperation and assistance in furthering the continuance of the educational program as outlined, with the hope that this objective will be applicable to all Station and General Hospitals.

"In view of the present emergency, your Committee feels that modification of the present program of the American College of Physicians and any suggestions for new activities should have careful and mature study. It is suggested that any action towards a change in any of these policies be considered a responsibility of this Committee, and, in view of the present emergency, that that Committee study thoughtfully and carefully any activity of the College in order to report regularly these activities to the Board of Regents.

"Your Committee approves the suggestions and recommendations of the Committee on Educational Policy and its recommendations concerning the improvement of medical libraries in Station and General Hospitals.

"In view of the fact that the United States at the present time is at War, it is highly important that the American College of Physicians continue its close relationship with its members, that it use its influence in exerting every effort toward the preservation of American institutions and the high ideals for which the American College of Physicians stands. It is contemplated that this College will carry on its activities as best it possibly can under the present emergency conditions. It is conceived that certain inevitable circumstances may arise which may curtail certain of our activities, but those activities may be curtailed in amount, but not in principle. It is believed that the Postgraduate Courses as outlined by our Committee are feasible and quite worth while. We hope that our program will continue along the high standards which have been established over this long period of years. Nothing else would be in keeping with the traditions which have been established by those who have gone before in this, our organization.

Respectfully submitted,

JAMES E. PAULLIN, *Chairman*
Committee on Survey and Future Policy"

By resolution, the above report was adopted seriatim and in its entirety.

President Lee called for the report of the House Committee, Dr. William D. Stroud, Chairman.

DR. STROUD: "The three paintings in the series, 'Pioneers of American Medicine,' entitled 'Beaumont and St. Martin,' 'Osler at Old Blockley' and 'The Conquerors of Yellow Fever,' were loaned to the College Headquarters through the courtesy of John Wyeth and Brother, in order to show what has been accomplished and can be done in producing original paintings depicting some epoch in American Medicine.

"No report has yet been received from the American Physicians Art Association, through which Dr. E. E. Woldman, F.A.C.P., Cleveland, offered a prize for the production of a painting acceptable to the College. However, no adequate time has yet elapsed, because the offer was made only in the spring of 1941, and the Association has not since held a meeting.

"*The College Headquarters*—There is nothing in particular to report, other than the fact that the Headquarters has been maintained in excellent condition with minor improvements here and there. Financial report for the year 1941 will show that the total cost of the Headquarters, including janitorial services, all equipment for the Executive Offices, maintenance, heat, light, gas and water, insurance and taxes, will be somewhat less than $5,000.00. We may reasonably expect some increase in maintenance with War conditions and higher prices of fuel. During the coming year the exterior woodwork should be painted. During the past summer, a further reduction in real estate assessment on the College Headquarters has been obtained, namely, from $39,700.00 to $30,200.00. At the time the Headquarters was purchased in 1936, the assessment was $65,000.00.

"*404–12 S. 42nd Street*—The adjoining property, extending to Osage Avenue from the College line, was purchased on July 11, 1941, with the approval of the Executive Committee of the College. The purchase price was $9,000.00, but the additional costs for taxes, settlement, commission, etc., brings the total expenditure to $9,540.28. The property was assessed at $23,300.00 at time of purchase, but this assessment has since been reduced to $17,200.00. It has been the hope of the House Committee that this property could be resold at book value to the National Board of Medical Examiners and the American Board of Surgery for their headquarters, thus establishing a small 'medical center' here. Although there have been numerous meetings and inspections, no definite developments have been reported to date."

President Lee called for the report of the Committee on Advertisements and Commercial Exhibits, Dr. George Morris Piersol, Chairman.

"DR. PIERSOL: "This Committee has not met, but our deliberations have been carried on largely by mail and telephone. We have passed upon a number of requests for exhibit space at the Annual Meeting. The difficulties, so far as advertising in the ANNALS is concerned, are not great, because we follow certain regulations already adopted by our Committee and apply the rules of the Council on Pharmacy and Chemistry of the American Medical Association to pharmaceutical advertisements. The Committee, in certain instances, has gone further in its restrictions on advertisements than most other medical journals, including those published by the American Medical Association. In spite of opportunities to accept very advantageous advertising contracts, as for example a double-page spread monthly of a cigarette advertisement, the Committee has refused the contracts, because it has considered them irrelevant to the practice of Internal Medicine and derogatory to the dignity of the journal."

President Lee requested report from the Treasurer, Dr. William D. Stroud.

DR. STROUD: "The income of the College for 1941, with estimations for the month of December, will be approximately $116,000.00, $3,000.00 more than estimated. The gross expenditures for 1941, also with estimations for December, will be approximately $92,000.00, leaving a surplus of about $24,000.00. The College operated at approximately $9,000.00 below its budget.

"The book value, or purchase price, of its security holdings is:

Endowment Fund	$120,763.57
General Fund	93,034.72
	$213,798.29, Total

"The present cash value of these securities was on December 11, 1941, $206,381.88, or a depreciation of only slightly over $7,000.00.

"The College employs a competent firm of investment counselors at a relatively small cost of about $400.00 per annum, and receives frequent surveys of its security holdings, which are reviewed periodically by the Finance Committee of the College.

"We believe the financial condition of the College sound and satisfactory. The accounts, as usual, will be audited by a certified public accountant at the end of the year, and his statements published in the ANNALS."

On motion by Dr. Cocke, seconded by Dr. Pepper and regularly carried, the Treasurer's report was accepted and filed.

President Lee then called for the report of the Finance Committee, Dr. O. H. Perry Pepper, Chairman.

"The Finance Committee of the American College of Physicians met at the College Headquarters on December 13, 1941. Drs. Bruce and Pepper of the Committee were present, Dr. Stone being delayed on account of bad weather. The Treasurer and Executive Secretary were also present.

"The Committee begs to report:

(1) Drexel & Co. have proved satisfactory Investment Counselors and Custodians. Their charge has been $425.00 a year less than our previous advisers.

(2) The Finance Committee recommends that no change be made in the present rules for dues of members entering active service in the armed forces. At present such officers pay $10.00 a year, as do the regular officers of the Army and Navy. Attention of the members will be drawn on the bills and in the ANNALS of their right to have any individual case considered by the Regents.

(3) One such case is that of Dr. H. B. Kirkland, of New York City, who has requested the waiving of his dues during the term of his service with the American Hospital in Britain. The Finance Committee recommends the waiver of his dues for the period.

(4) A year ago the Regents made available for one year $10,000.00 for research desired by the Army or Navy. One-half was allocated to Cohn of Harvard for work on blood substitutes. The remaining $5,000.00 has not been allocated. In view of the fact that adequate funds for medical research have been appropriated by the Government, the Finance Committee recommends that the Regents declare the term of the offer expired and so notify the National Research Council.

(5) Also an appropriation was made a year ago to finance the work of Dr. Paullin in evaluating the self designated internists of the country. This extremely valuable work has now been extended to the whole field of the practitioners of medicine. The sum appropriated last year has been expended, and the Finance Committee recommends that an additional $1,000.00 be made available to Dr. Paullin for the completion of this task.

(6) The Finance Committee reports that figures supplied by the Executive Secretary show that of the more than $32,000.00 in closed banks in Pittsburgh, all but $1,391.19 has been recovered.

(7) Without going into details, the Finance Committee wishes to inform the Regents concerning the suggestions of Drexel & Co., dated December 11, 1941:

(*a*) That the College sell some $25,000.00 railroad and utility bonds and purchase $25,000.00 additional Defense Bonds. The bonds to be sold form almost one-half of our non-governmental bond holdings of about $55,000.00. While we already hold $62,000.00 governmental bonds, the exchange suggested could be carried out with a slight gain over original prices, but with a loss of annual income of some $350.00.

The Committee did not approve the suggestion, feeling that it was quite proper to hold in a total account of about $214,000.00, about one-quarter in bonds of this general character.

The Committee approved the recommendation for the sale of our holding of preferred stock of the Central New York Power Co.

No changes were suggested in the common stock group. Drexel & Co.'s advice on the holding uninvested of most of the $22,000.00 cash balance was approved.

(8) The Finance Committee recommends to the Regents the approval of the budgets prepared by the Executive Secretary for the year 1942, with the addition of $1,000.00 for the evaluation task of Dr. Paullin.

The total budget requests for 1942 equal $86,176.50, plus the $1,000.00 for Dr. Paullin, $87,176.50. This, compared with the 1941 budget of $100,644.00, is $13,467.50 less.

The explanation of this difference lies chiefly in three items in the 1941 budget: (*a*) $10,000.00 appropriated for research; (*b*) $2,500.00 to Dr. Paullin; (*c*) over $700.00 for purchase of new addressograph.

Other changes deserving mention include a further reduction in the taxes on the College Headquarters, and suggested increases in salaries for the Headquarters, totalling $710.00 and an increase of $1,700.00 in the estimated cost of publication of the ANNALS.

The expenditures for 1941, with December estimated, show close adherence to the budget figures.

The expected surplus for 1941 is $24,193.25. The Finance Committee recommends the salary increases suggested by the Executive Secretary and the adoption of all the suggested budgets.

The Executive Secretary will be glad to present any desired details.

(9) The Finance Committee should report that it gave its approval of the investment of a part of surplus funds in the purchase of the house and property adjoining on the south the present College Headquarters.

The price was $9,000.00 and taxes, insurance, etc., brought the all-inclusive price to $9,540.28. Reduction in tax assessment has already been obtained.

The Finance Committee recommends that no hasty sale or decision be made in the disposition of this property. Offers received would net the College a small profit, but the purpose of the purchase was more to insure the control of the future dignified disposition of this neighboring property.

(10) The Committee recommends to the Regents the appropriation of $50.00 from this year's funds to Mr. M. R. Wiley, the houseman of the College Headquarters, as a bonus.

(11) The Committee also recommends to the Board of Regents an appropriation of $100.00 for secretarial expenses for the Advisory Committee on Postgraduate Courses.

Respectfully submitted,
JAMES D. BRUCE
CHARLES T. STONE
O. H. PERRY PEPPER, *Chairman*
Committee on Finance"

By resolution regularly carried, the report of the Committee on Finance was adopted seriatim and in its entirety.

Dr. Lee called for a report of the Committee on Constitution and By-Laws, Dr. Ernest E. Irons, Chairman.

Dr. Irons had no report.

At this point, President Lee reported upon the arrangements for the forthcoming Annual Session of the College in St. Paul, saying that activities were going on apace and that if the Regents had any desire to modify the program or arrangements they should consider them at this time. He expressed the opinion that the College should continue to function in its ordinary fashion, and he, as President, saw no reason why the College should not proceed in the usual manner with all arrangements.

At this point, Dr. Lee introduced Dr. John A. Lepak, General Chairman of the St. Paul Session.

DR. LEPAK: "Mr. Chairman and members of the Board of Regents, immediately upon the selection of St. Paul as the meeting city for 1942, the President and the Executive Secretary conferred with me and we all started immediately in preparing the future plans. Before I returned to St. Paul from the Boston Session, I had an opportunity to meet many of the experienced officers from former meetings of the College and some of the Governors, and thus obtained some advance information as to how to proceed. On return to St. Paul, we immediately organized our committees on the same pattern they had been organized previously, with some minor changes. We then wrote a letter to each member of the Board of Governors and of the Board of Regents to determine if he would participate in a clinic and what subject he would select. In a very short time, forty-four acceptances were received. We then organized the men in St. Paul, Minneapolis, Rochester and some from Wisconsin and elsewhere, and in a short time our clinic program was well organized. As for the panels, I appointed a chairman, who selected a few out-of-town men for the panel program and soon had that program completed. We selected five hospitals in St. Paul, with a capacity of 1,600 seats daily, and added the University Hospital and the College of Science Building, next to the University, with an additional seating capacity of 500 seats, so we have available accommodations for 2,100 men at the clinics daily.

"Our Auditorium is one of the best Auditoriums in the United States, and in it we have ample space to seat 2,800 people for the General Sessions. We have adequate room for exhibits, panel programs and also a restaurant, so that attendants may not have to leave the Auditorium. . . ."

Dr. Lepak then read portions from his clinic program, saying it was a fair sample of the program for one day. He likewise read a portion of the panel program, and outlined the general program for entertainment and other activities.

President Lee thanked Dr. Lepak for his labors and congratulated him, on behalf of the Regents and himself, for the excellency of the program organized.

Continuing, President Lee said, "The obligation of the President has been to secure the papers for the General Sessions, the Morning Lectures and the Convocation Address. For the latter, we have secured Dr. William de B. MacNider, whose subject will be 'A Consideration of the Factor of Change in the Animal Organism.' The Morning Lectures we have attempted to make provocative, and we have taken as a general title 'Medical Horizons.' Those who will give lectures we have asked not to be didactic, but rather to attempt to look at the horizons and perhaps a little bit beyond the horizons, to be imaginative and stimulating. It is practically necessary and very fitting, of course, that one of the men to deliver a Morning Lecture should be Dr. Cohn, who received the grant of money for research from the College. Exactly how much he will be able to say concerning his particular researches is not yet known, but it is assured that he will have something interesting. . . ."

Dr. Lee read portions of his program of General Sessions and summarized his arrangements. A new feature, as a precautionary measure against some speakers being unable to attend, Dr. Lee had established a group of papers under the title "To be read if time permits." He expressed the intention to follow the general procedure of the College from former years, and said that papers would not be presented unless the speaker himself were present. He expressed optimism toward the prospects of a very successful meeting in St. Paul, and assured the Board that the program would be of very great scientific and professional excellence.

President Lee then asked for the report of the Executive Secretary.

SECRETARY LOVELAND: "My report is restricted to arrangements for the St. Paul Session. The customary business arrangements, including those for meetings of the various Boards, the exhibit, etc., have been made. While there has been no advance indication of dropping off of the exhibitors, it is quite possible that because of the location and the War developments, the exhibit may be slightly smaller. The Officers, Regents and Governors of the College will be housed at the Hotel Lowry, but both the Hotel Lowry and the Hotel St. Paul have been appointed joint headquarters, in order that a fairly adequate number of rooms shall be available to accommodate all in attendance."

President Lee asked for a report from the Marshal of the Convocation, Dr. Reginald Fitz.

DR. FITZ: "Mr. President, I am sorry to say that my hypersensitiveness to having the names of the newly elected Fellows read aloud is apparently something to which I must get accustomed. After the meeting last year, I thought it would be wise if I could get some evidence on the matter, and accordingly I sent letters asking various gentlemen whether they did or did not like to hear the names read. 372 replies were received; of these 60 per cent felt that a substitute should be devised for the reading aloud of the names, and 40 per cent voted that the names should be read aloud as heretofore. There seemed to be no particular prejudice one way or the other, but what did impress me more than anything else were the letters that came in from several people defending the reading aloud of the names. I have brought two of those letters which I wish to present. The first is from a younger man, inducted a few years ago:

> 'My thought on this matter is that this meeting is designed particularly for the benefit of the newly elected Fellows and to impress them with the significance of their entrance into the College. This should be an event to be remembered, and from my own experience, I can assure you that it was much more impressive to hear my own name read there before a large assembly as a newly-elected Fel-

low of the College than it was to hear the out-going President review the history of the College, a procedure which has been done so often that everybody knows it by heart, or hear the speakers discuss some subject in which none of the newly-elected members are interested.'

"The second expresses about the same idea, making a point that to a good many of the younger men the Convocation and the presentation of their names are obviously an event worth while, and because of that feeling, I am convinced the only thing to do is to keep on with reading the names, but to try to do it better than ever before."

DR. PEPPER: "Since Dr. Fitz has been interested in the Convocations they have improved markedly. He has accomplished much."

At this point, President Lee brought up the matter of the Regents-Governors Dinner. It was announced that the customary Dinner would be tendered on the part of the College to the Officers, Regents and Governors, with a limited number of guests, on Sunday evening, April 19, at St. Paul before the formal opening of the Session. At these dinners the President presides and matters of particular interest to the College are discussed.

Dr. Cocke, Chairman of the Board of Governors, reported to the Regents that the College Governor for Maine had offered to resign because he had been called to active military service, but stationed not far from Portland. Dr. Cocke had advised him that so long as he could still function as Governor, he should continue.

PRESIDENT LEE: "There is a somewhat incongruous situation in regard to two committees—the Executive Committee and the Committee on Survey and Future Policy. The Executive Committee has been a sort of an ad interim committee, theoretically composed of men within a short distance of the College Headquarters. When the Executive Committee meets and votes, it is more often done by mail, and it does not appear, at least to me, that this is quite a valuable function, yet the Executive Committee is empowered with practically all the authority of the Board of Regents, with the exception of electing new members and adjusting fees and dues. It has seemed to me that, as in other businesses, the Executive Committee ought to be the Committee of Survey and Future Policy. It should be the steering committee. It should be the committee that builds up the agenda for the two meetings of the Board of Governors. It might have an occasional meeting, or it could transact emergency business by telephone or by correspondence. These are some reflections that I indulged in when I had to appoint these two committees, the Executive Committee and the Committee on Future Policy, and while I am out of order in making these remarks, and I will not make any motion, I would like to know what the Board of Regents thinks about it. Any action taken would not become effective until the committees are appointed at the next Annual Session. If the Regents feel inclined to amalgamate these two committees into a real Executive Committee, it would seem better administration to me."

DR. STROUD: "Mr. President—I would like to move that these two committees be combined, with instructions that the Executive Committee become active in the future policy and planning of the College."

DR. PEPPER: "I would like to ask the Executive Secretary to read that part of the Constitution or By-Laws which govern the composition of the Executive Committee."

Secretary Loveland read the section from the By-Laws.

DR. PEPPER: "The chief change would be the omission of certain individuals who have continued their interest in the College after their term of service on the Board of Regents has, of necessity, expired. That may not be a strong argument, and except for that, I think the scheme is a very good one. This is the only drawback. The duties of the Executive Committee with regard to survey and future policy are implied in the wording of the By-Laws. It is a perfectly reasonable and normal thing to do, and I was in favor of the change until I thought that it would eliminate all except

members of the Board of Regents. I do not know whether it is a good idea to have retired Regents stay on the Survey Committee, but that is what we have done. They have sort of grown into the position like senior statesmen."

DR. STROUD: "My original motion was not seconded, so I should like to change it, namely, that a resolution be presented at the next meeting of the Annual Business Meeting, outlining the duties of the Executive Committee and, if necessary, enlarging the Committee, not limiting it to the Board of Regents, and providing for its appointment by the President rather than by the Board of Regents."

DR. PEPPER: "I will second Dr. Stroud's motion."

SECRETARY LOVELAND: "I believe it would be a mistake to change the personnel of the Executive Committee, adding men outside of the Board of Regents. There have been in the early years of the College many occasions when there was real serious work for the Executive Committee, and those occasions might arise again. With a mixed membership, some of whom are inexperienced in the work of the Board of Regents, it might prove a rather serious objection. Probably Dr. Piersol and some of the other men who were active fifteen or so years ago will remember that the whole reorganization was brought about not in the Board of Regents, but in the Executive Committee. Those changes and reorganization plans could not have been carried through effectively in the Board of Regents as then constituted, but it was accomplished in the smaller and more effective Executive Committee. I feel that your present Constitution and By-Laws should not be altered. I am wholly favorable to assigning the duties of your Committee on Survey and Future Policy to your Executive Committee. The Executive Committee as now constituted is a protection, although it may not be called upon to function."

On investigation of the present personnel of the Committee on Survey and Future Policy, it was found that no member would be affected by the change other than Dr. James Alex. Miller. It was further learned that the organization of the Committee on Future Policy and Survey was not set up in the By-Laws, but under resolution of the Board of Regents.

Dr. Stroud withdrew his motion and Dr. Pepper his second. Dr. Piersol pointed out that the correction of the present fault is simple and that all that would be necessary is to disband the present Committee at the end of the present year and refer all such matters in the future to the Executive Committee.

Dr. Fitz suggested that the Executive Committee could be nominated by the regular Nominating Committee, rather than directly elected by the Board of Regents. Dr. Cocke pointed out that that would require amendments to the By-Laws. Dr. Morgan expressed doubt as to whether the existence of the two Committees had caused the College to suffer in any respect, and said there appeared to be no very pressing reason for making the change at this time.

On motion by Dr. Piersol, seconded by Dr. Blake, it was moved that it be the sense of this meeting that the Committee on Survey and Future Policy be not reappointed for the next year.

DR. PAULLIN: "Mr. President, I would not want to be placed, as the incoming President who has to appoint these committees, in the very embarrassing position of having to leave Dr. Miller off the Committee and not reappoint a Committee on Survey and Future Policy. If it is the sense of the Board of Regents that the Executive Committee can perform these functions, then I feel that that should be a function of that Committee. As a matter of fact, I think we have an excessive number of committees in the College and their duties at times overlap, and I think that as soon as we can eliminate some of these committees, so many men serve on several of them, while the College may not function better, there will be more time for meetings and for the transaction of business in the committees. Of the three or four committees on which I have served, one has had no report, the Executive Committee. I am not at all sure but that the present duties of the Committee on Survey and Future Policy

belong to the Executive Committee of this College. I feel like Dr. Lee, that the Committee on Survey and Future Policy is a problem which directly concerns the Executive Committee. And then, too, the Committee on Medical Preparedness—there is no more necessity for that, and I think these committees could be merged into one, and then you would have plenty of time to transact business and not have to run from one committee to another. I am in favor of Dr. Piersol's motion, without prejudice to any one who is on the Committee."

Dr. Piersol revised his resolution to read,

RESOLVED, that it be the sense of this meeting that the Committee on Survey and Future Policy be not reappointed for the next year, and that its functions and duties be definitely assigned to the Executive Committee.

The addition was accepted by Dr. Blake, the seconder, put to a vote and carried, with one dissenting vote.

President Lee asked if any one had any matter that he wished to present for consideration.

SECRETARY LOVELAND: "Our Board of Regents has been requested to examine a medical motion picture, with the thought that the College might engage in a further function of examining and approving medical motion pictures in the field of Internal Medicine. This particular motion picture was entitled 'The Principle of Allergy,' and was submitted by one of our Fellows. It has been examined by a few of our Regents. It was considered to be somewhat of elementary nature and to disclose nothing that the Board of Regents would be interested in approving or disapproving."

On motion by Dr. Stroud, seconded by Dr. Fitz and regularly carried, it was

RESOLVED, that the Board of Regents are not ready to commit themselves to any action whatsoever, inasmuch as it has not heretofore engaged in this activity and has not yet been impressed with the need.

President Lee declared the meeting adjourned at 3:30 p.m.

Attest: E. R. LOVELAND,
Executive Secretary

ST. PAUL *

SOME OF ITS EDUCATIONAL, CIVIC AND RELIGIOUS INSTITUTIONS

Nestled in a curve of the majestic Mississippi, the City of St. Paul, one of Minnesota's oldest, takes pride in her pioneer heritage and in her steady growth since the roaring days of the covered wagon and Indian massacres.

Now a quiet, dignified city—Capital of the great State of Minnesota—St. Paul has one of the most corrupt-free governments in the Nation.

1—Saint Paul's Cathedral.

* The Twenty-sixth Annual Session of the American College of Physicians will be held in St. Paul, April 20–24, 1942.

Crime has been reduced to a minimum under a commission form of government; the city's financial position has been brought into healthy balance, and a new wave of prosperity has been engendered by the nation's rearmament program.

Railroading and wholesale houses, together with a considerable manufacturing business, make up the bulk of the city's economy. St. Paul also is a trucking center of importance.

With a population approaching the 300,000 mark, St. Paul and surrounding areas support four colleges and one university within the city

2—Minnesota State Capitol, Saint Paul.

limits. The city is the headquarters of the Roman Catholic Archdiocese of Minnesota and the Cathedral,[1] rising high over the skyline, is one of the largest churches on the North American continent. More than 300 feet high, it seats 4,000 worshipers.

Also looming large on the St. Paul horizon is the Minnesota State Capitol,[2] of the Roman Classic type, built of Georgia marble and designed by the eminent architect, Cass Gilbert. Completed and furnished at a cost of $4,500,000, the huge domed building is considered an outstanding example of its architectural type.

Those who are familiar with the tomb of Napoleon in the Church of the Invalides in Paris cannot fail to see a resemblance in the setting of the

rotunda, with the second floor's circular corridors and balustrades looking down on the main floor.

Newest, and perhaps most striking government building in St. Paul, is the City Hall-Court House,[3] an imposing structure situated on the bank of the Mississippi River and blending well with the city's modern skyline.

3—Saint Paul City Hall and Court House.

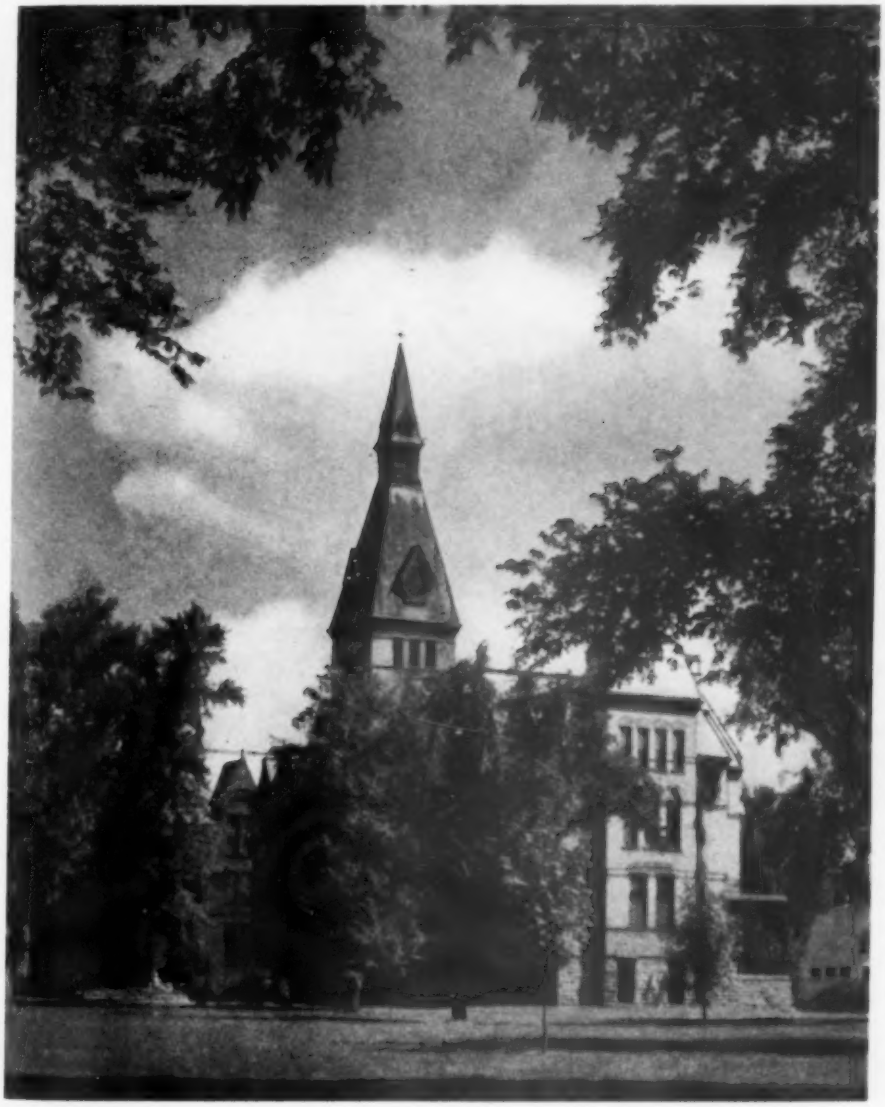
The building consists of an 18-story tower, surrounded by three stepped-back stories which spread out over the entire city block which the building occupies.

Not only is the City Hall-Court House a structure of dignity and beauty, it is the architect's dream of functional design, having within its

4—The First National Bank of Saint Paul.

walls more than 80 per cent usable space as contrasted with the usual 40 per cent in most public buildings.

Outstanding feature of the building is the huge onyx Indian, standing



5—Old Main, Hamline University.

three stories high, symbolizing the God of Peace, holding a pipe in one hand and with the other extended in a gesture of friendliness. Dedicated to American war veterans, the statue is symbolic of the thought that out of conference and understanding comes the hope of peace in the world.

The First National Bank building [4] is the first visible landmark of St. Paul, whether you approach the city by train, highway or airplane. Its 32-story tower structure, standing clear and white by day, marked by a huge illuminated "1st" sign by night, is the city's tallest. The building is 402 feet high, with an added 100 feet of sign structure on its pinnacle.

St. Paul's only university, Hamline,[5] is situated in what is known locally as the "Midway District." Chartered in 1854, Hamline's first building stood in a wheat field by itself. Now the Hamline community is filled with lovely homes and the University itself is a cluster of buildings on a beautiful campus. There are nine in all, grouped around "Old Main."

The Library and Norton Field House are on Snelling Avenue, with Science Hall and the Union near-by. Hamline church is a part of the

6—Kirk Hall, Dormitory for Men, Macalester College.

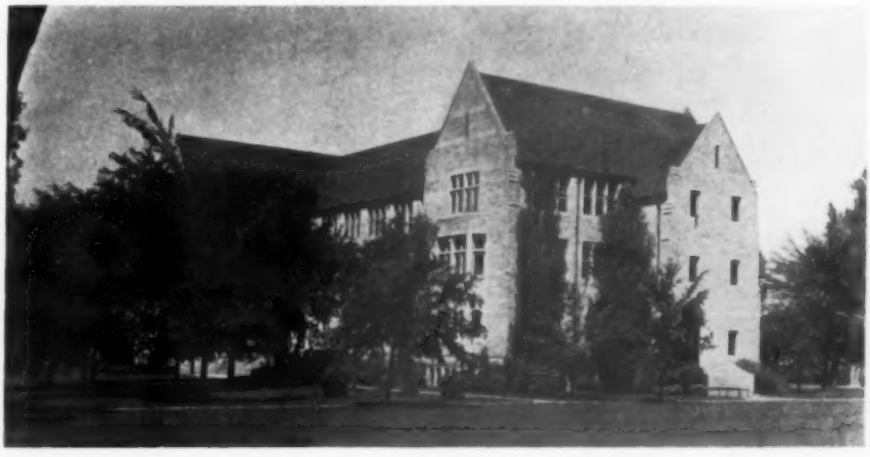
architectural scheme and is used for chapels, concerts, and religious activities. The Manor House is a residence for women and Goheen Hall, a residence for men, while adjacent to the campus is the home of the university president and seven other residences used by fraternities, co-operatives and homes for women. The athletic field and tennis courts are within a block of the campus. Improvements to laboratories were made last year and new equipment added to make Hamline a thoroughly up-to-date university.

Pre-medicine and law and preëngineering are among the courses provided at Hamline. The music department is unusual and annually attracts large numbers of students. The a cappella choir of 60 voices is outstanding.

Macalester College,[6] located a mile and a half south on Snelling Avenue from Hamline, was founded in 1885 by Dr. Edwin Duffield Neill, pioneer

Presbyterian minister and educator. Christian in purpose, non-sectarian in instruction and attitude, Macalester provides courses culminating in Bachelor of Arts degrees.

The College of St. Thomas,[7] founded in the same year as Macalester, was the inspiration of the late great Archbishop Ireland. Originally in two departments, classical and theological, the College was divided when the late James J. Hill gave the archdiocese funds with which to establish the St. Paul Seminary. St. Thomas offers a four-year curriculum in which the first two years are devoted to general education on the college level and the last two years to the field of concentration, thus preparing students for graduate study in English, foreign languages, biology, chemistry, mathematics, history, social sciences, economics, business administration, philosophy or education.



7—College of St. Thomas, Main Building.

In addition to the College of St. Thomas, the institution also houses the St. Thomas Military Academy, whose aim is " the highest excellence in the training of young men." It enjoys the highest ranking given by the War Department, belonging to the coveted " MS " division.

What St. Thomas College is in the field of men's education, St. Catherine's College[8] is in the women's field. The College of St. Catherine, named for the Roman Catholic church's philosopher saint, Catherine of Alexandria, was founded in 1911 by the Sisters of St. Joseph of Carondelet. Since its establishment, the College has occupied a leading position in the educational development of the Northwest.

Concordia College, St. Paul's smallest, is a branch of Concordia of Moorhead, situated on the Red River of the North, some 250 miles west and slightly north of the Twin Cities. A Lutheran institution, it offers four-year Bachelor of Arts degrees.

In the field of sports, St. Paul and its Twin City, Minneapolis, offer a wide variety of entertainment, both in spectator and active sport. Eleven golf courses are within easy reach of downtown St. Paul—Town and Country, one of the finest in the nation; Somerset, University, Midland Hills, Hillcrest and Southview, all conveniently located only a short distance out-

8—Mendel Hall, The College of St. Catherine, Saint Paul, Minnesota (Science Building).

side the city limits; White Bear on the lake of the same name; Keller, a county-owned course, and Highland, Como, and Phalen, all city-owned clubs inside the city limits.

St. Paul is a member of the American Association of Baseball Clubs, and for those who enjoy fishing there are many fine lakes within a few miles of the loop district, and more than 10,000 in all of Minnesota—"land of the sky-blue water."